



**Eur päisches
Patentamt**

**European
Patent Office**

**Office européen
des brevets**

Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99116533.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 19/10/01
LA HAYE, LE

THIS PAGE BLANK (USPTO)



Eur päisches
Patentamt

European
Patent Office

Office européen
des brevets

Blatt 2 d r Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 99116533.3
Demande n°:

Anmeldetag:
Date of filing: 24/08/99 ✓
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
Chen, Una, Biochemistry Inst., University of Giessen
35392 Giessen
GERMANY

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Method for growing stem cells

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:
State:
Pays:

Tag:
Date:
Date:

Aktenzeichen:
File no.
Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:

C12N5/06, C12N5/08, C12N5/10, C12N15/63, C12N15/85, A61K48/00, A61K35/12

Am Anmeldetag benannte Vertragsstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR ✓
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

THIS PAGE BLANK (USPTO)

EPO-Munich
51

24. Aug. 1999

Method for growing stem cells

The present invention is related to a method for growing stem cells.

Stem cells are commonly defined as cells which exist for the lifetime of an organism and are able to undergo symmetric and/or asymmetric divisions, to give rise to further stem cells (for preservation of the stem cell pool) and to more differentiated cells with defined life-time (for organ-specific functions). Due to this unique property they are ideal vehicles for somatic gene therapy. They would maintain the transgene for the life-time of the tissue and the organism, and would carry the transgene expression into the differentiated cells. Stem cells may be totipotent (e.g. embryonic stem cells), pluripotent (e.g. hematopoietic stem cells) or unipotent (e.g. keratinocytes, muscle precursor cells).

Although being the aim of many research projects, it has until now being very difficult to grow stem cells, especially lineage-committed stem cells, thereby controlling expansion and differentiation of the stem cells.

The present invention provides a method for growing stem cells comprising the steps of

- providing stem cells with supporters said supporters being genetically modified in order to provide externally regulatable interactions between the supporters and the stem cells;
- applying an external signal for starting or stopping the interactions.

According to the present invention, stem cells are co-incubated with supporters. These supporters are genetically modified to allow a regulatable interaction with the

- 2 -

stem cells. These interactions between the supporters and the stem cells are externally regulatable. "Externally regulatable" defines that the interaction between the supporters and the stem cells is regulated from outside of the supporters.

Preferably, the interactions are based on the secretion or display of substances. These substances, which are secreted or displayed by the supporters control the development of the stem cells. The expansion or differentiation of the stem cells is indirectly controlled by the regulatable interactions of the supporters.

Preferably as external signals may serve the addition or removal of substances, heat, light, sound and/or electromagnetic waves. The only requirement is that these external signals are able to regulate the interactions between the supporters and the stem cells.

Preferably, the supporters are cells. They may be stem cells or non-stem cells. In a preferred embodiment these supporters are forming a micro-environment.

The supporting cells can be further transformed with foreign genes to express a gene product of interest e.g. a protein of the clotting cascade, insulin, enzymes growth factors or the like.

It is believed that the supporters form a micro-environment thus providing cytokines and adhesion molecules as well as direct contact between the stem cells and the supporters. Suitable supporters are skin cells, lung cells, bone marrow stroma cells, or tissue cells.

Suitable secreted or displayed substances are cell based growth factors, protein growth factors, interleukines.

In particular, the supporters are genetically modified with a vector comprising a gene for the substances, e.g. interleukines, protooncogenes, oncogenes, cell cycle control genes, and/or cell based growth factors and a regulatable expression system. A preferred regulatable expression system is the regulatable tetracycline expression system.

Preferred vectors for the transformation of the supporters are the vectors selected from the group consisting of pRetro-tet-off-E6/E7, pRetro-tet-off-U19-tsA58, pUHD15.1- β -gal-NeoR, pUHD10.3-TGF β 3, pUHD10.3-hIL3, pUHD10.3-hIL6, pD12YCVJC-long-CNTF, pD12YCVJC-long-GDNF, pD12YCVJC-short-CNTF and pD12YCVJC-short-GDNF.

Details on these vectors can be found in the examples and the figures.

Cell lines obtainable by genetically modification of cells with the vectors of the present invention form part of the invention.

The present invention further provides a method of curing diseases by gene therapy and/or cell therapy which diseases are related to insufficient, lack or disorder of stem cells, by administering to patients in need thereof, supporters being genetically modified in order to provide externally regulatable interactions between the supporters and the stem cells. Furthermore, any disease related to insufficient expression or activity of a protein or enzyme can be treated by administering supporters and/or stem cells after expansion ex vivo.

Fig. 1 shows the appearance of hIL-3, depending on the addition/removal of doxycycline in vivo.

Fig. 2 shows the shows the appearance of hIL-6 depending on the addition/removal of doxycycline in vivo.

- 4 -

Fig. 3 shows the cloning of growth factor genes.

Fig. 4 to **12** show the sequences of vectors.

The method of the present invention is further explained by the following example:

Example

hIL6 containing transgenic-keratinocytic stem cells support the growth of (sister) keratinocytic stem cells in culture: In these sets of experiments, ELISA assays were performed with supernates obtained from one hIL6 of construct teto-hIL6 containing keratinocytic cell clone derived from a CMV-tTA x teto-SV40 T antigen transgenic mouse, either cultured alone, or with doxycycline included in the culture for 0-12h, 25-50h. This experiment is to test whether the secretion of cytokines affects by doxycycline in culture.

hIL6 promotes the growth of CMV-tTA x teto-SV40Tag transgenic keratinocytic stem cell line drastically by increasing cell numbers. At the presence of hIL6, the growth arrest at G1 compartment is abolished, and cells continue to grow in the presence of doxycycline.

The level of hIL6 in the supernates was slightly inhibited at time point of 12h, and increase again at 50h, up to the level of the control cells, i.e., without doxycycline. Thus, hIL6-containing clone continued to secrete hIL6 despite of the fact that doxycycline was included in the culture.

The data are interpreted as follow: Engineered stem cells support the growth of sister stem cells (internally or externally) in vitro by the combination of the following two mechanisms:

- 5 -

(1) The hIL6 engineered keratinocytic stem cells secrete hIL6 into supernate, target and promote the growth of sister keratinocytic stem cells - an external/heterocrine mechanism.

(2) The gene product of hIL6 engineered keratinocytic stem cells, acts intracytoplasmically, and promotes the growth of itself - an internal/autocrine mechanism.

1. In both events, hIL6 is able to maintain skin in the keratinocytic stem cells compartment, upon the withdraw of doxycycline.

Cytokine-containing keratinocytic stem cells and tracheal epithelial stem cells secrete cytokines known to support the growth of hematopoietic stem cells (HSC):

Using hIL3, hIL6, flk2/flt3Ligand to support the growth of HSC for several weeks in culture, and in comparing to that of stroma cell lines in supporting HSC, has been performed. In the literature there are many published data showing that hIL3, hIL6, flk2/flt3Ligand are essential to support the growth of HSC. These data show that these cytokines are essential in maintaining HSC in culture, and in increasing the transduction efficiency of retroviruses into HSC in the two chamber culture system where the experiments were performed and described in the literature.

Keratinocytic stem cell lines and tracheal epithelial stem cell lines were established from CMV-tTA x tetO-CMVm-SV40Tag double transgenic mice (from H. Bujard and S. Efrat).

Stem cells are supported by cytokine-containing transgenic stem cells: in vivo using immunoincompetent mice (nu/nu mice): It is for the purpose of somatic

- 6 -

delivery of growth factors essential for maintenance of human hematopoietic stem cells (HSC) in recipient hosts. The cytokines constructed shown to be functional for HSC are hIL3, hIL6, and flk2/flt3Ligand, and thus are used further for in vivo experiments (below).

Teto-hIL6, teto-hIL3 containing transgenic keratinocytic and tracheal epithelial stem cells derived from CMV-tTA x teto-CMVm-SV40Tag double transgenic mice were pre-cultured on DED (denuded dermis from human cosmetic operation) and implanted subcutaneously (flip-in) into immunoincompetent mice (nude mice).

Blood samples from such nude mice were collected from a tail vein of mice periodically. Sera were separated from blood clots. ELISA tests were performed on serum samples collected. After cytokines were demonstrated to appear in blood, such nude mice ingested doxycycline (1mg/ml) included in the drinking water and blood collected at the time points indicated. As indicated in figures 1 (hIL3) and 2 (hIL-6), hIL3 and hIL6 are shown to appear in the blood reaching a significant amount (14.7 pg/ml for hIL3, 15.9 pg/ml for hIL6), and they were decreased when doxycycline was included the drinking water. Upon removal of doxycycline, hIL3 and hIL6 were shown to increase to higher levels again (41.2 pg/ml for hIL3, and 14.5pg/ml for hIL6). Upon reingestion of doxycycline, the levels of cytokines were shown to decrease to zero.

The mice survive over the 5-6months of experiment without any sign of illness due to the implantation of engineered mouse stem cells delivering human cytokines. The pattern can be cyclic. It is predicted that the protocol will work similarly in the SCID-NOD mice. Thus, in nude mice, we show that the secretion of cytokines such as hIL3 and hIL6 into the blood stream is regulated by doxycycline in the drinking water.

In summary, the above protocol of somatic engineering of immuno-incompetent mice with regulatable delivery of growth factors has been tested and shown to be deliverable to high titers in nu/nu mice. The growth of transgenic keratinocytes and lung epithelial cells, and the delivery of cytokines are shown to be subjected to the regulation of doxycycline (in culture of some cells, such as HETA cells but not other cells, such as a hIL6-containing keratinocytic cell line, when doxycycline is included in the medium); and in vivo when included in the drinking water.

The principle of this protocol can also apply to the support of the growth of stem cells of any kind, such as neural and glial stem cells, in immuno-incompetent mice, as a novel diagnostic tool for evaluating the preclinical and clinical protocols.

Establishment and commercialization of SCID-NOD-hu systems as diagnostics for growth and evaluation of self-renewal property of human neuronal and glial stem cells, clinical protocol and for drug targeting:

The keratinocytic stem cell line and tracheal epithelial stem cell line derived from CMV-tTAXtetoCMVm-SV40Tag double transgenic mice are used in this type of experiment. These cell lines are inserted with cytokine constructs for the somatic delivery of neurotropic factors essential for the survival and maintenance of human adult brain stem cells in recipient hosts. The cytokines constructed are pD12YCV-JC-driven GDNF and CNTF. The transgenic tracheal epithelial stem cells are pre-cultured on DED (dead de-epidermized dermis) and implanted subcutaneously (flip-in) (in the head region) into SCID-NOD mice. The growth of transgenic lung keratinocytic stem cells and epithelial cells, and the delivery of cytokines have been shown to be subjected to the regulation of doxycycline in culture and in vivo when included in the drinking water. The mice survive over the months of experiment without any sign of illness due to the implantation of engineered mouse cells deliv-

- 8 -

ering human cytokines. The principle of the protocol will work similarly in the SCID-NOD mice for human neurotrophic factors.

Protocol for construction of pD12JCVPLong-CNTF plasmid

Similar strategy and construction protocols held for pD12JCVPLong-GDNF, pD12JCVPshort-CNTF, pD12JCVPshort-GDNF.

1. pD12JCVPLong vector (from E. Beck and J. Henson) was linearized upon NsiI restriction enzyme.
2. The sticky ends of the vector were filled using Klenow fragments of E. coli polymerase I.
3. Digestion of the linearized pD12JCVPLong vector with restriction enzyme XhoI.
4. After digestion, the DNA sample was subjected to gel electrophoresis in 0.8% preparative agarose gel to obtain ca. 6.3 kb DNA fragment (pD12JCVPLong x NsiI/XhoI).
5. pBS-hCNTF-079 vector (from E. Beck) was linearized with restriction enzyme NotI.
6. The termini of the linearized pBS-hCNTF-079 vector was filled with Klenow fragment of E. coli DNA polymerase I in order to obtain the blunt-end.
7. The linearized and blunt-ended (pBS-hCNTF-079 x NotI) was digested with SmaI.

8. After digestion, the DNA sample was subjected to gel electrophoresis in 0.8% preparative agarose gel and the 2469 bp DNA fragment containing CNTF gene was isolated.
9. The blunt- and sticky ended (CNTF x NotI/SaI) fragment (from step 8) was ligated with complementary blunt- and sticky-ended (pD12JCVPLong x NsiI/XhoI) (from step 4) vector.
10. VXL1-blue competent bacteria *E. coli* was transformed with DNA (from step 9), and ampicillin resistant clones were selected, and characterized to be correct.

Protocol for construction of pRetro-OFF-E6E7 plasmid:

1. pLXSNE6E7 vector (from D. Galloway) was linearized upon EcoRI restriction enzyme digestion.
2. The sticky ends of the vector was filled using Klenow fragments of *E. coli* DNA polymerase I.
3. The termini of the linearized pLXSNE6E7 was ligated with synthetic adaptor (XhoI-NotI-BglII) purchased from Roth, Karlsruhe.
4. The newly adapted-[pLXSNE6E7 x NotI/BamHI] (step 3) was digested with NotI and BamHI.
5. After digestion, the DNA sample was subjected to gel electrophoresis in 1% preparative agarose gel to obtain ca. 830 bp fragment of [E6E7 x NotI/BamHI].
6. pRetro-OFF vector was digested with NotI and BamHI.

- 10 -

7. The fragment of [E6E7 x NotI/BamHI] was then inserted into the [pRetro-OFF vector x NotI/BamHI] (step 6).
8. XL1-blue competent bacteria E.coli were transformed with the construct from step 7. Ampicillin resistant clones were selected and characterized to be correct.

Protocol-2 for construction of pRetro-OFF-U19tsA58 plasmid:

1. pZipNEOSV(x) vector (from P. Jat) was digested with BamHI restriction enzyme.
2. After digestion, the DNA sample was electrophoresed in 0.8 % preparative agarose gel to obtain ca 2.6 kb DNA fragment (U19tsA58 x BamHI).
3. pRetro-OFF vector was linearized with restriction enzyme BamHI.
4. The terminal of the linearized pRetro-OFF vector was dephosphoried with Shrimp Alkaline Phosphatase (USB) from Amersham.
5. The fragment of (U19tsA58 x BamHI) (from step 2) was then inserted into the (pRetro-OFF vector x BamHI) (from step 4).
6. The XL1-blue competent bacteria E. coli was transformed with DNA (from step 5), and ampicillin resistant clones were selected, and characterized to be correct.

Protocol for the construction of pUHD-transactivator vectors:

A. Transactivator, pUHD15.1-pCMV- α TA- β -gal-neomycin plasmid:

1. pUHD15.1 (from H. Bujard) was linearized using BamHI restriction enzyme.

- 11 -

2. 5' -end was dephosphorized using phosphatase, and the DNA sample was subjected to gel electrophoresis in 1% preparative agarose gel to obtain ca. 7255 bp fragment of (pUHD15.1BamHI).
3. IRES- β geo fragment which contains lacZ+neo (Ca 3050 bp)) was obtained from another plasmid (ptetotsA58IRES β geo) (from H. Schoeler) using BamHI restriction enzyme digestion.
4. After digestion, the DNA sample was subjected to gel electrophoresis in 1% preparative agarose gel to obtain ca. 3050 bp fragment of (IRES- β geoBamHI).
5. The fragment of (IRES- β geoBamHI) (step 4) was then inserted into the (pUHD15.1BamHI) (step 2) β .
6. XL1-blue competent bacteria E. coli were transformed with the construct from step 5. Ampicillin resistant clones were selected and characterized to be correct.

Protocol for the construction of pUHD-responder vectors:

B. Responder pUHD10.3 cytokine plasmids:

1. The multiple cloning site (MCS) of responder pUHD10.3 (from H. Bujard) was linearized using EcoRI and SacII (for hIL6), or EcoRI and BamHI (for hIL3), or EcoRI and XbaI (for TGF β 3) restriction enzymes.
2. After digestion, the individual DNA sample was subjected to gel electrophoresis in 1% preparative agarose gel to obtain ca. 3150 bp fragment of DNA.
3. Fragments of cDNA coding for hIL6 (EcoRI-SacII), hIL3 (EcoRI-BamHI), TGF β 3 (EcoRI-XbaI) were obtained from the original supplier (A. Bernad, Ge-

- 12 -

netic Institute, ATCC), and individual restriction enzyme digested as indicated in the original publications.

4. After digestion, the DNA sample was subjected to gel electrophoresis in 1% preparative agarose gel to obtain ca. 600 bp fragment of hIL6 (EcoRI-SacII), ca. 475 bp fragment of hIL3 (EcoRI-BamHI), and ca. 1233 bp fragment of TGF β 3 (EcoRI-XbaI).
5. The fragment coding for the respective cytokine gene (step 4) was then inserted into the responder pUHD10.3 EcoRI-SacII (for hIL6), or EcoRI-BamHI (for hIL3), or EcoRI-XbaI (for TGF β 3) (step 2).
6. XL1-blue competent bacteria *E. coli* were transformed with the construct from step 5. Ampicillin resistant clones were selected and characterized to be correct.

- 13 -

EPO-Munich
51

24. Aug. 1999

Claims

1. A method for growing stem cells comprising the steps of
 - providing stem cells with supporters said supporters being genetically modified in order to provide externally regulatable interactions between the supporters and the stem cells;
 - applying an external signal for starting or stopping the interactions.
2. The method of claim 1 wherein the interactions are based on secretion or display of substances.
3. The method of any of the claims 1 or 2 wherein the supporters are modified for the secretion or display of substances under control of a promoter.
4. The method of any of claims 1 to 4 wherein the external signal is the addition or removal of substances, heat, light, sound and/or electromagnetic waves.
5. The method of any of claims 1 to 4, wherein the supporters are non-stem cells.
6. The method of any of claims 1 to 4, wherein the supporters are stem cells.
7. The method of any one of claims 1 to 6, wherein the supporters are forming a micro-environment.

- 14 -

8. The method of any one of claims 1 to 7, wherein the supporters are skin cells, lung cells, bone marrow stroma cells or tissue cells.
9. The method of any one of claims 1 to 8, wherein the supporters are secreting or displaying cell based growth factors, protein growth factors and/or interleukines.
10. The method of any one of claims 1 to 8, wherein the supporters are transformed by a vector comprising a gene for interleukines, protooncogenes, oncogenes, cell cycle control genes, and/or cell based growth factors as well as a regulatable expression system, such as a tetracycline regulatable expression system.
11. A vector selected from the group consisting of pRetro-tet-off-E6/E7, pRetro-tet-off-U19-tsA58, pUHD15.1- β -gal-NeoR, pUHD10.3-TGF β 3, pUHD10.3-hIL3, pUHD10.3-hIL6, pD12YCVJC-long-CNTF, pD12YCVJC-long-GDNF, pD12YCVJC-short-CNTF and pD12YCVJC-short-GDNF.
12. A supporter cell being genetically modified in order to provide a regulatable secretion and/or a display of substances of the supporters.
13. A method of curing diseases by gene therapy and/or cell therapy which diseases are related to insufficient and/or lack and/or disorders of stem cells, by administering to patients in need thereof, supporters being genetically modified in order to provide externally regulatable interaction between supporter cells and stem cells.

- 15 -

14. Cell lines obtainable by transforming cells with the vector according to claim 11.

EPO-Munich
51

24. Aug. 1999

- 16 -

Abstract

A method for growing stem cells comprising the steps of

- providing stem cells with supporters said supporters being genetically modified in order to provide externally regulatable interactions between the supporters and the stem cells;
- applying an external signal for starting or stopping the interactions.

EPO-Munich
51

24. Aug. 1999

- 1/35 -

pg/ml Blut (hIL-3)

hIL-3

Doxycycline-Test in vivo (hIL-3)

Doxy-Zugabe

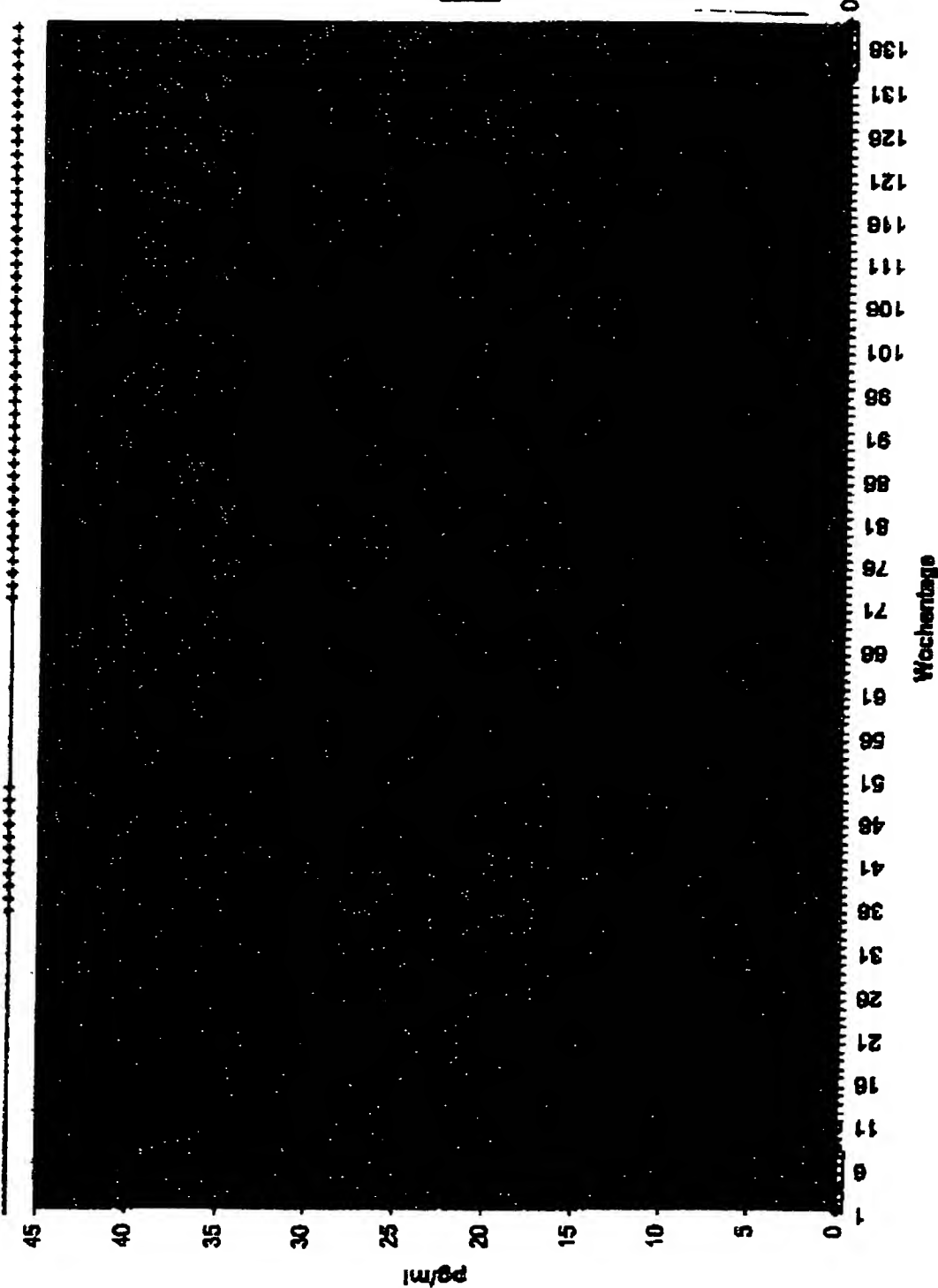


Fig. 1

- 2/35 -

hIL-6

Doxycycline-Test in vivo (hIL-6)

Doxy-Zugabe

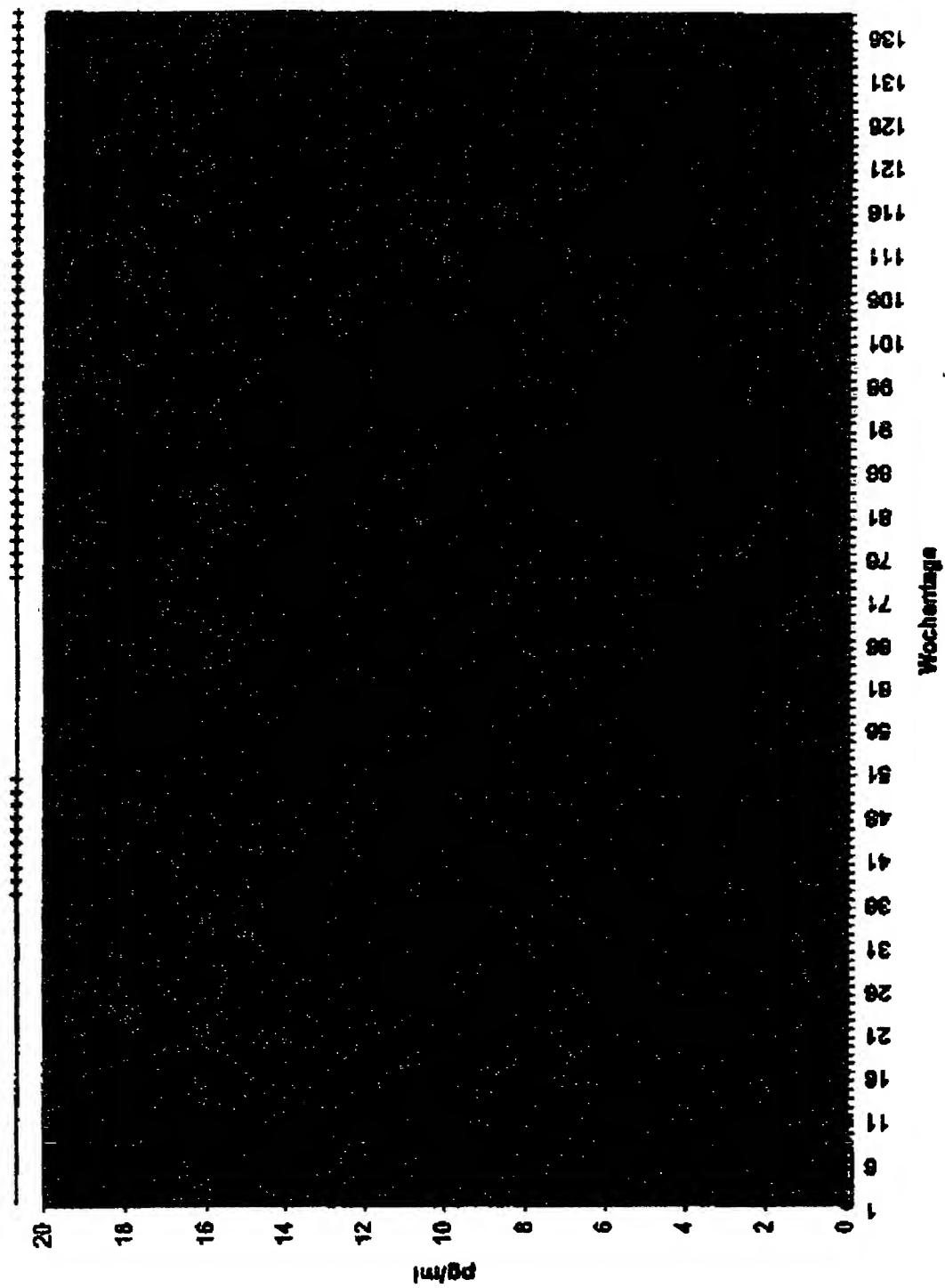


Fig. 2

- 3/35 -

Cloning of growth factor genes

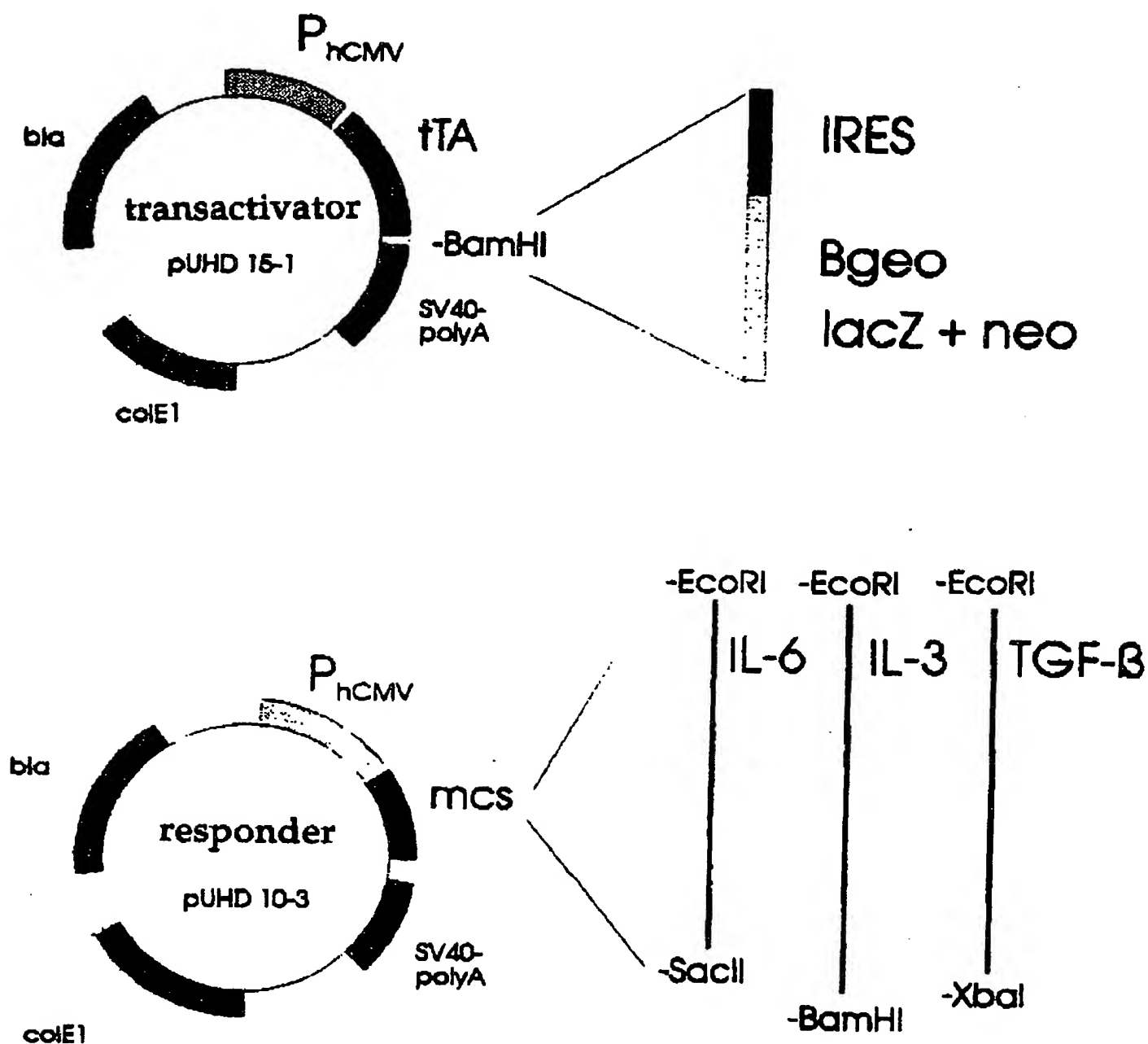


Fig. 3

Printed: 19-10-2001

SPEC

99116533

- 4/35 -

pb12JCVP1ong-hCNTT

Length: 7969 July 22, 1999

1 GCTAGCGATT TAGGTGACAC TATAGAATAG ATctcg enn nGTCACCCCT
 51 AGAGTCGAGC TGTGACGGTC CTTACAATGA AATGCANCTG GGTATCTTC
 101 TTCCTGATGG CAGGGGTTAC AGGTAAGGGG CTCCCAAGTC CCAAACCTGA
 151 GGGTCCATAA ACTCTGTGAC AGTGGCAATC ACTTTGCCTT TCTTTCTACA
 201 GGGGTGAATT CGGCTTTCAC AGAGCATTCA CCGCTGACCC CTCACCGTCG
 251 GGACCTCTGT AGCCGCTCTA TCTGGCTAGC AAGGAAGATT CGTTCAGACC
 301 TTGACTGCTC TTACGGAATC CTATGTAAGT TGCCTATTTT GCTGTTATCT
 351 GTTTTCCCTT CATCTTTTTT GATCCAGCAA CTTACCATCA CGCATCAGCT
 401 CCATTACCAA TTGTGAAAGC TCTAATCATA TAGTCATTCA TATAGGTTAT
 451 TTGACATGGG CCCTTCCCTT GAGGAACCC ATGTGACTTT ATTTTCTTCC
 501 TCTGGGCTGT TTAGGAGATG AAGTTACTTG AATGAGAAAA TATATATGGA
 551 GTTCTAGAAA GGATTGGTTT ATATGTCTTG GAGGCTATTT CAAAATTTAT
 601 TTGGCCATAT ATTCTGAATA CTACCTAGAA CAGATTAGCC ATGGGCCCTH
 651 TGGGTNTTC ATAAGCCATT GTTCTGAANT TTTTAGCTT TGTAATGAA
 701 AGGTTTATGG GATAOGAAGA GTNCTATGAA CGTGGGAGGA ATTTGTAAAT
 751 CCTACCAATT TNTNCTATAT AGCATTAGCC CCCACCTTTT ANTATTCTGC
 801 ATCAAAAGTA AGATTGTGTC TAAAGAGAAA GGTNAGCTAT CAAAAGGACT
 851 CCTATAANAT TCNTTGGAAA CTNTTGGAAH TGTCAAATTT NTTTGAGCTA
 901 ATTNTTGGAG TTCCAAANTT TGTCTTNTNA CAGTNAAGGG GGANCCCCAT
 951 TCANATTTNC CCCCCTNNNG ANAATGCTTG GGGGAAAAAA CCTNCCAACC
 1001 CCNTTGTGGG ANGAAGTTTT TTTAANNTTT TAAAGCTNGN NGAAACNGGN
 1051 TTTTAAATTT TTGGGNCNAN CGCCTNTCCC CGGTACCAGG AAAATCAGGA
 1101 CCTNTTTTTG GGGNNGNGCN CCHACNGGGG GGNAAAANGG GAAATTCNT
 1151 CANAAAAAAT CTTTTCCGnn nnnngtgaag catcagggcc tgaacaagaa
 1201 catcaacctg gactctgogg atgggatgcc agtggcaagc actgatcagt
 1251 ggagtgaact gaccgaggca gagogactcc aagagaacct tcaagcttat

Fig. 4

1301 cgtaccttcc atgttttgtt ggcaggctc ttagaagacc agcagggtgca
1351 ttttaccceca acegaagggtg acttecatca agctatacat acccttcttc
1401 tccaagtegc tgcctttgca taccagatag aggagttaat gatactcctg
1451 gaatacaag tcccccgcaa tgaggctgat gggatgccta ttaatgttgg
1501 agatgggtggc ctctttgaga agaagctgtg gggcctaaag gtgctgcagg
1551 agctttcaca gtggacagta aggtccatcc atgaccttcg ttccatttct
1601 tctcatcaga ctgggatccc agcacgtggg agccattata ttgctaacaa
1651 caagaaaatg tagnnnnngc ggcctgcgcc gtctttcccg acgttaaagg
1701 gatgaaacca caagacttac cttcgctcgg aagtaaaacg acaaacacac
1751 acagttttgc cctgtttcat gagaaatggg acgtctgcgc acgaaacggc
1801 cctgcgcttg aggaggactt gtacaaacac gatctatgca ggtttcccca
1851 actgacacaa accgtgcaac ttgaaactcc gcctgggtctt tccagggtcta
1901 gaggggtaac attttgtact gtgtttgact ccacgctcga tccactagcg
1951 agtgtttagta gccgtactgc tgtctcgtag cggagcatgt tggccgtggg
2001 aacacctcct tggtaacaag gaccacggg gccgaaagcc atgtcctaac
2051 ggacccaaca tgtgtgcaac ccagcacgg cagctttact gtgaaacca
2101 cttcaagggtg acattgatac tggtaactca acactggtga caggctaagg
2151 atgcccttca ggtaccccg aagtaacaagc gacctcggg atctgagaag
2201 gggactggga cttctttaaa gtgcccagtt taaaagctt ctacgcctga
2251 atagggtgacc ggaggccggc acctttcctt ttataaccac tgaacacatg
2301 gaagacgcca aaacataaa gaaaggcccg gcgccattct atcctctaga
2351 ggatggaacc gctggagagc aactgcataa ggctatgaag agatacggcc
2401 tggttcctgg aacaattgct ttacagatg cacatatcga ggtgaacatc
2451 acgtacgchg aatacttcga aatgtccgtt cggttggcag aagctatgaa
2501 acgatatggg ctgaatacaa atcacagaat cgtcgtatgc agtgaaaact
2551 ctcttcaatt ctttatgccg gtgttgggcg cgttatTTAT cggagttgca
2601 gttgcgcccc cgaacgacat ttataatgaa cgtgaattgc tcaacagtat
2651 gaacatttcg cagcctaccg tagtgtttgt ttccaaaag gggttgcaaa

Fig. 4

Printed:19-10-2001

SPEC

99116533

2701 AAATTTTGAA CGTGCAAAAA AAATTACCAA TAATCCAGAA AATTATTATC
2751 ATGGATTCTA AAACGGATTA CCAGGGATTT CAGTCGATGT ACACGTTTCGT
2801 CACATCTCAT CTACCTCCCG GTTTTAATGA ATACGATTTT GTACCAGAGT
2851 CCTTTGATCG TGACAAAACA ATTGCACTGA TAATGAATTC CTCTGGATCT
2901 ACTGGGTTAC CTAAGGGTGT GGGCCTTCCG CATAGAACTG CCTGCGTCAG
2951 ATTCTCGCAT GCCAGAGATC CTATTTTGG CAATCAAATC ATTCCGGATA
3001 CTGCGATTTT AAGTGTTGTT CCATTCCATC ACGGTTTTGG AATGTTTACT
3051 ACACTCGGAT ATTTGATATG TGGATTTTGA GTCGTCTTAA TGTATAGATT
3101 TGAAGAAGAG CTGTTTTTAC GATCCCTTCA GGATTACAAA ATTCAAAGTG
3151 CGTTGCTAGT ACCAACCCTA TTTTCATTCT TCGCCAAAAG CACTCTGATT
3201 GACAAATACG ATTTATCTAA TTTACACGAA ATTGCTTCTG GGGGCGCACC
3251 TCTTTCGAAA GAAGTCGGGG AAGCGTTGTC AAAACGCTTC CATCTTCCAG
3301 GGATACGACA AGGATATGGG CTCACTGAGA CTACATCAGC TATTCTGATT
3351 ACACCCGAGG GGGATGATAA ACCGGGCGCG GTCGGTAAAG TTGTTCCATT
3401 TTTTGAAGCG AAGGTTGTGG ATCTGGATAC CGGGAAAACG CTGGGCGTTA
3451 ATCAGAGAGG CGAATTATGT GTCAGAGGAC CTATGATTAT GTCCGGTTAT
3501 GTAAACAATC CGGAAGCGAC CAACGCCTTG ATTGACAAGG ATGGATGGCT
3551 ACATTCTGGA GACATAGCTT ACTGGGACGA AGACGAACAC TTCTTCATAG
3601 TTGACCGCTT GAAGTCTTTA ATTAAATACA AAGGATATCA GGTGGCCCCC
3651 GCTGAATTGG AATCGATATT GTTACAACAC CCCAACATCT TCGACGCGGG
3701 CGTGGCAGGT CTTCCCGACG ATGACGCGCG TGAACCTCCC GCGCGCGTTG
3751 TTGTTTTGGA GCACGGAAAG ACGATGACCG AAAAAGAGAT CGTGGATTAC
3801 GTCGCCAGTC AAGTAACAAC CGCGAAAAAG TTGCGCGGAG GAGTTGTGTT
3851 TGTGGACGAA GTACCGAAAG GTCTTACCG AAAACTCGAC GCAAGAAAAA
3901 TCAGAGAGAT CCTCATAAAG GCCAAGAAGG GCGGAAAGTC CAAATTGTAA
3951 AATGTAAC TG TATTACGCGA TGACGAAATT CTTAGCTATT GTAATGACTC
4001 TAGAGGATCT TTGTGAAGGA ACCTTACTTC TGTGGTGTGA CATAATTGGA
4051 CAAACTACCT ACAGAGATTT AAAGCTCTAA GGTAAATATA AAATTTTAA

Fig. 4

4101 GTGTATAATG TGTAAACTA CTGATTCTAA TTGTTTGRT ATTTTAGATT
4151 CCAACCTATG GAACTGATGA ATGGGAGCAG TGGTGGAATG CCTTTAATGA
4201 GGAAACCTG TTTTGCTCAG AAGAAATGCC ATCTAGTGAT GATGAGGCTA
4251 CTGCTGACTC TCAACATTCT ACTCCTCCA AAAAGAAGAG AAAGGTAGAA
4301 GACCCCAAGG ACTTTCCTTC AGAATTGCTA AGTTTTTTGA GTCATGCTGT
4351 GTTTAGTAAT AGAACTCTTG CTGCTTTGC TATTACACC ACAAAGGAAA
4401 AAGCTGCACT GCTATACAAG AAAATTATGG AAAATATTC TGTAACCTTT
4451 ATAAGTAGGC ATAACAGTTA TAATCATAAC ATACTGTTTT TTCTTACTCC
4501 ACACAGGCAT AGAGTGTCTG CTATTAATAA CTATGCTCAA AAATTGTGTA
4551 CCTTTAGCTT TTTAATTTGT AAAGGGGTTA ATAAGGAATA TTTGATGTAT
4601 AGTGCCCTGA CTAGAGATCA TAATCAGCCA TACCACATTT GTAGAGGTTT
4651 TACTTGCTTT AAAAACCTC CCACACCTCC CCCTGAACCT GAAACATAAA
4701 ATGAATGCAA TTGTTGTTGT TAACTTGTTT ATTGCAGCTT ATAATGGTTA
4751 CAAATAAAGC AATAGCATCA CAAATTCAC AAATAAAGCA TTTTTTTCAC
4801 TGCATTCTAG TTGTGGTTTG TCCAACTCA TCAATGTATC TTATCATGTC
4851 TGGATCCCGG GGTCCCTATA GTGAGTCGTA TTAGCTTGGC GTAATCATGG
4901 TCATAGCTGT TTCCTGTGTG AAATTGTTAT CCGCTCACAA TTCCACACAA
4951 CATACGAGCC GGAAGCATAA AGTGTAAGC CTGGGGTGCC TAATGAGTGA
5001 GCTAACTCAC ATTAATTGCG TTGCGCTCAC TGCCCGCTTT CCAGTCGGGA
5051 AACCTGTCGT GCCAGCTGCA TTAATGAATC GGCCAACCGG CGGGGAGAGG
5101 CGGTTTGCGT ATTGGGCGCT CTTCCGCTTC CTCGCTCACT GACTCGCTGC
5151 GCTCGGTCGT TCGCTGCGG CGAGCGGTAT CAGCTCACTC AAAGGCGGTA
5201 ATACGGTTAT CCACAGAATC AGGGGATAAC GCAGGAAAGA ACATGTGAGC
5251 AAAAGGCCAG CAAAAGGCCA GGAACOGTAA AAAGGCCGCG TTGCTGGCGT
5301 TTTTCCATAG GCTCCGCCCC CCTGACGAGC ATCACA AAAA TCGACGCTCA
5351 AGTCAGAGGT GGCGAAACCC GACAGGACTA TAAAGATACC AGGCGTTTCC
5401 CCCTGGAAGC TCCCTCGTGC GCTCTCCTGT TCGACCCTG CCGCTTACCG
5451 GATACCTGTC CGCCTTCTC CCTTCGGGAA GCGTGGCGCT TTCTCAATGC

Fig. 4

Printed: 19-10-2001

SPEC

99116533

5501 TCACGCTGTA GGTATCTCAG TTCGGTGTAG GTCGTTGCT CCAAGCTGGG
5551 CTGTGTGCAC GAACCCCCCG TTCAGCCCCG COGCTGCGCC TTATCCGGTA
5601 ACTATCGTCT TGAGTCCAAC CCGTAAGAC ACGACTTATC GCCACTGGCA
5651 GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC
5701 AGAGTTCTTG AAGTGGTGGC CTAACACGG CTACACTAGA AGGACAGTAT
5751 TTGGTATCTG CGCTCTGCTG AAGCCAOTTA CCTTCGGAAA AAGAGTTGGT
5801 AGCTCTTGAT CCGGCAAACA AACCACCGCT GGTAGCGGTG GTTTTTTTGT
5851 TTGCAAGCAG CAGATTACGC GCAGAAAAAA AGGATCTCAA GAAGATCCTT
5901 TGATCTTTTC TACGGGGTCT GACGCTCAGT GGAACGAAAA CTCACGTTAA
5951 GGGATTTTGG TCATGAGATT ATCAAAAAGG ATCTTCACCT AGATCCTTTT
6001 AATTAAAAA TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT
6051 GGTCTGACAG TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC
6101 TGTCTATTTT GTTCATCCAT AGTTGCTGA CTCCCGCTCG TGTAGATAAC
6151 TACGATACCG GAGGGCTTAC CATCTGGCCC CAGTGTGCA ATGATACCGC
6201 GAGACCCACG CTCACCGGCT CCAGATTAT CAGCAATAAA CCAGCCAGCC
6251 GGAAGGGCCG AGCGCAGAAG TGGTCTGCA ACTTTATCCG CCTCCATCCA
6301 GTCTATTAAT TGTTGCCGGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA
6351 GTTTCGCAA CGTTGTTGCC ATTGCTACAG GCATCGTGGT GTCACGCTCG
6401 TCGTTTGTA TGGCTTCATT CAGCTCCGT TCCCAACGAT CAAGGCGAGT
6451 TACATGATCC CCCATGTTGT GCAAAAAGC GGTAGCTCC TTCGGTCTCT
6501 CGATCGTTGT CAGAAGTAAG TTGGCCGCAG TGTATCACT CATGGTTATG
6551 GCAGCACTGC ATAATTCTCT TACTGTCTAG CCATCCGTAA GATGCTTTTC
6601 TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG TGTATGOGGC
6651 GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGCGCCACAT
6701 AGCAGAACTT TAAAAGTGCT CATCATTTGA AAACGTTCTT CGGGGCGAAA
6751 ACTCTCAAGG ATCTTACCGC TGTGAGATC CAGTTCGATG TAACCCACTC
6801 GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG
6851 TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGGCGAC

Fig. 4

6901 ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT TATTGAAGCA
6951 TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTGA ATGTATTTAG
7001 AAAAATAAAC AAATAGGGGT TCCGCGCACA TTTCCCOGAA AAGTGCCACC
7051 TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACCTAT AAAAATAGGC
7101 GTATCACGAG GCCCTTTTCGT CTCGCGCGTT TCGGTGATGA CGGTGAAAC
7151 CTCTGACACA TGCAGCTCCC GGAGACGGTC ACAGCTTGTC TGTAAGCGGA
7201 TGCCGGGAGC AGACAAGCCC GTCAGGGCGC GTCAGCGGT GTTGGCGGGT
7251 GTCGGGGCTG GCTTAACTAT GCGGCATCAG AGCAGATTGT ACTGAGAGTG
7301 CACCATATGC GGTGTGAAAT ACCGCACAGA TGOGTAAAGGA GAAAATACCG
7351 CATCAGGCGC CATTCGCCAT TCAGGCTGCG CAACTGTTGG GAAGGGCGAT
7401 CGGTGCGGGC CTCTTCGCTA TTACGCCAGC TGGCGAAAGG GGGATGTGCT
7451 GCAAGGCGAT TAAGTTGGGT AACGCCAGGG TTTTCCCACT CACGACGTTG
7501 TAAAACGACG GCCAGTGAAT TTCGACCTGC AGTCGACAGA AGCCTTACGT
7551 GACAGCTGGC GAAGAACCAT GGCCAGCTGG TGACAAGCCA AAACAGCTCT
7601 GGCTCGCAA ACATGTTCCC TTGGCTGCTT TCCACTTCCC CTTGTGCTTT
7651 GTTTACTTGT GTCAGCTGGT TGGCTCCCTA GGTATGAGCT CATGCTTGGC
7701 TGGCAGCCAT CCAGTTTATG CCAGCTCTGC TTTGTTTACT TGTGTCAGCT
7751 GGTTGGCTCC CTAGGTATGA GCTCATGCTT GGCTGGCAGC CATCCAGTTT
7801 TAGCCAGCTC CTCCCTACCT TCCCTTTTTT TTATATATAC AGGAGGCCGA
7851 GGCCGCCTCC GCCTCCAAGC TTA CTCAGAA GTAGTAAGGG CGTGGAGGCT
7901 TTTTAGGAGG CCAGGGAAAT TCCCTTGTTT TCCCTTTTTT TGCAGTAAT
7951 TTTTGCTGCA AAAAGCTAA

Fig. 4

- 10/35 -

JCVPlong-gdnf Length: 6971 June 8, 1999 16:42 Type: N Check: 3588 ..

```

1  GCTAGCGATT TAGGTGACAC TATAGAATAG ATCCCCATGA AGTTATGGGA
51  TGTGCTGGCT GTCTGCCTGG TGCTGCTCCA CACCGCGTCC GCCTTCCCGC
101 TGCCCGCCGG TAAGAGGCCT CCGGAGGCGC CCGCCGAAGA CCGCTCCCTC
151 GGCCGCCGCC GCGCGCCCTT CGCGCTGAGC AGTGACTCAA ATATGCCAGA
201 GGATTATCCT GATCAGTTCG ATGATGTCAT GGATTTTATT CAAGCCACCA
251 TTAAGAGACT GAAAGGTCA CCAGATAAAC AAATGGCAGT GCTTCCTAGA
301 AGAGAGCGGA ATCGCCAGGC TGCAGCTGCC AACCCAGAGA ATTCCAGAGG
351 AAAAGGTCGG AGAGGCCAGA GGGGCAAAAA CCGGGGTGTG GTCTTAACTG
401 CAATACATTT AAATGTCACT GACTTGGGTC TGGGCTATGA AACCAAGSAG
451 GAACTGATTT TTAGGTACTG CAGCGGCTCT TGCGATGCAG CTGAGACAAC
501 GTACGACAAA ATATTGAAAA ACTTATCCAG AAATAGAAGG CTGGTGAGTG
551 ACAAGTTAGG GCAGGCATGT TGCAGACCCA TCGCCTTTGA TGATGACCTG
601 TCGTTTTTAG ATGATAACCT GGTTTACCAT ATTCTAAGAA AGCATTCCGC
651 TAAAGGTGTG GGATGTATCT GACTGGTGCG CCGTCTTTCC CGACGTTAAA
701 GGGATGAAAC CACAAGACTT ACCTTCGCTC GGAAGTAAAA CGACAAACAC
751 ACACAGTTTT GCCCGTTTTT ATGAGAAATG GGACGTCTGC GCACGAAACG
801 CGCCGTCGCT TGAGGAGGAC TTGTACAAAC ACGATCTATG CAGGTTTCCC
851 CAACTGACAC AAACCGTGCA ACTTGAAACT CCGCCTGGTC TTTCCAGGTC
901 TAGAGGGGTA ACATTTTGTA CTGTGTTTGA CTCCACGCTC GATCCACTAG
951 CGAGTGTTAG TAGCGGTACT GCTGTCTCGT AGCGGAGCAT GTTGGCCGTG
1001 GGAACACCTC CTTGGTAACA AGGACCCACG GGGCCGAAAG CCATGTCCTA
1051 ACGGACCCAA CATGTGTGCA ACCCCAGCAC GGCAGCTTTA CTGTGAAACC
1101 CACTTCAAGC TGACATTGAT ACTGGTACTC AAACACTGGT GACAGGCTAA
1151 GGATGCCCTT CAGGTACCCG GAGGTAACAA GCGACACTCG GGATCTGAGA
1201 AGGGGACTGG GACTTCTTTA AAGTGCCGAG TTTAAAAAGC TTCTACGCCT
1251 GAATAGGTGA CCGGAGGCCG GCACCTTTCC TTTTATAACC ACTGAACACA
1301 TGGAAGACGC CAAAAACATA AAGAAAGGCC CGGCGCCATT CTATCCTCTA
1351 GAGGATGGAA CCGCTGGAGA GCAACTGCAT AAGGCTATGA AGAGATACGC
1401 CCTGGTTCTT GGAACAATTG CTTTTACAGA TGCACATATC GAGGTGAACA
1451 TCACGTACGC GGAATACTTC GAAATGTCCG TTCGGTTGGC AGAAGCTATG
1501 AAACGATATG GGCTGAATAC AAATCACAGA ATCGTCTGAT GCAGTGAAAA
1551 CTCTCTTCAA TTCTTTATGC CGGTGTGTTG CGCGTTATTT ATCGGAGTTG
1601 CAGTTGGCGC CGCGAACGAC ATTTATAATG AACGTGAATT GCTCAACAGT
1651 ATGAACATTT CGCAGCCTAC CGTAGTGTTC GTTTCCAAAA AGGGGTGTCG
1701 AAAAATTTTG AACGTGCAAA AAAAATTACC AATAATCCAG AAAATTATTA
1751 TCATGGATTG TAAACGGGAT TACCAGGGAT TTCAGTCGAT GTACACGTTT
1801 GTCACATCTC ATCTACCTCC CGGTTTTAAT GAATACGATT TTGTACCAGA
1851 GTCCTTTGAT CGTGACAAAA CAATTGCACT GATAATGAAT TCCTCTGGAT
1901 CTACTGGGTT ACCTAAGGGT GTGGCCCTTC CGCATAGAAC TGCCTGCGTC
1951 AGATTCTCGC ATGCCAGAGA TCCTATTTTT GGCATCAAAA TCATTCCGGA
2001 TACTGCGATT TTAAGTGTTG TTCCATTCCA TCACGGTTTT GGAATGTTTA
2051 CTACACTCGG ATATTTGATA TGTGATTTT GAGTCGTCTT AATGTATAGA
2101 TTTGAAGAAG AGCTGTTTTT ACGATCCCTT CAGGATTACA AAATTCAAAG
2151 TGCGTTGCTA GTACCAACCC TATTTTCATT CTTGCGCAAA AGCACTCTGA
2201 TTGACAAATA CGATTTATCT AATTACACG AAATTGCTTC TGGGGGCGCA
2251 CCTCTTTGCA AAGAAGTCGG GGAAGCGGTT GCAAAACGCT TCCATCTTCC
2301 AGGATACGTA CAAGGATATG GGCTCACTGA GACTACATCA GCTATTCTGA
2351 TTACACCCGA GGGGGATGAT AAACCGGGCG CGGTCGGTAA AGTTGTTCCA
2401 TTTTTTGAAG CGAAGGTTGT GGATCTGGAT ACCGGGAAAA CGCTGGGCGT
2451 TAATCAGAGA GGCGAATTAT GTGTCAGAGG ACCTATGATT ATGTCGGGTT
2501 ATGTAAACAA TCCGGAAGCG ACCAACGCCT TGATTGACAA GGATGGATGG
2551 CTACATCTCT GAGACATAGC TTAAGTGGAC GAAGACGAAC ACTTCTTCAT
2601 AGTTGACCGC TTGAAGTCTT TAATTAAATA CAAAGGATAT CAGGTGCCCC
2651 CCGCTCAATT GGAATCGATA TTGTTACAAC ACCCAACAT CTTCGACGCG
2701 GCGGTGGCAG GTCTTCCCGA CGATGACGCC GGTGAACTTC CCGCCGCCGT
2751 TGTTGTTTTG GAGCACGGAA AGACGATGAC GGAAAAAGAG ATCGTGGATT
2801 ACGTCGCCAG TCAAGTAACA ACCGCGAAAA AGTTGCGCGG AGGAGTTGTG
2851 TTTGTGGACG AAGTACCGAA AGGTCTTACC GGAAAACTCG ACGCAAGAAA
2901 AATCAGAGAG ATCCTCATAA AGGCCAAGAA GGGCGGAAAG TCCAAATTGT
2951 AAAATGTAAC TGTATTCAGC GATGACGAAA TTCTTAGCTA TTGTAATGAC
3001 TCTAGAGGAT CTTTGTGAAG GAACCTTACT TCTGTGGTGT GACATAATTG
3051 GACAAACTAC CTACAGAGAT TTAAGCTCT AAGGTAAATA TAAAATTTTT
3101 AAGTGTATAA TGTGTTAAAC TACTGATTCT AATTGTTTGT GTATTTTAGA
3151 TTCCAACCTA TGGAACGTAT GAATGGGAGC AGTGGTGGAA TGCCTTTAAT
3201 GAGGAAAACC TGTTTTGCTC AGAAGAAATG CCATCTAGTG ATGATGAGGC

```

Fig. 5

- 11/35 -

| | | | | | |
|------|-------------|-------------|-------------|------------|-------------|
| 3251 | TACTGCTGAC | TCTCAACATT | CTACTCCTCC | AAAAAAGAAG | AGAAAGGTAG |
| 3301 | AAGACCCCAA | GGACTTTCCT | TCAGAATTGC | TAAGTTTTTT | GAGTCATGCT |
| 3351 | GTGTTTAGTA | ATAGAACTCT | TGCTTGCTTT | GCTATTTACA | CCACAAAGGA |
| 3401 | AAAAGCTGCA | CTGCTATACA | AGAAAATTAT | GGAAAAATAT | TCGTAAACCT |
| 3451 | TTATAAGTAG | GCATAACAGT | TATAATCATA | ACATACTGTT | TTTTCTTACT |
| 3501 | CCACACAGGC | ATAGAGTGTC | TGCTATTAAT | AACTATGCTC | AAAAATTGTG |
| 3551 | TACCTTTAGC | TTTTTAATTT | GTAAGGGGGT | TAATAAGGAA | TATTTGATGT |
| 3601 | ATAGTGCCTT | GACTAGAGAT | CATAATCAGC | CATACCACAT | TTGTAGAGGT |
| 3651 | TTTACTTGCT | TTAAAAAACC | TCCACACCTT | CCCCCTGAAC | CTGAAACATA |
| 3701 | AAATGAATGC | AATTGTTGTT | GTAAACTTGT | TTATTGCAGC | TTATAATGCT |
| 3751 | TACAAATAAA | GCAATAGCAT | CACAAATTTT | ACAAATAAAG | CATTTTTTTT |
| 3801 | ACTGCATTCT | AGTTGTGGTT | TGTCCAAACT | CATCAATGTA | TCTTATCATG |
| 3851 | TCTGGATCCC | CGGGTCCCTA | TAGTGAGTCG | TATTAGCTTG | CGGTAATCAT |
| 3901 | GGTCATAGCT | GTTTCCTGTG | TGAAATTGTT | ATCCGCTCAC | AATTCCACAC |
| 3951 | AACATACGAG | CCGGAAGCAT | AAAGTGTAAG | GCCTGGGGTG | CCTAATGAGT |
| 4001 | GAGCTAACTC | ACATTAAATT | CGTTGCGCTC | ACTGCCCGCT | TTCCAGTCGG |
| 4051 | GAAACCTGTC | GTGCCAGCTG | CATTAATGAA | TCGGCCAAAC | CGCGGGGAGA |
| 4101 | GGCGGTTTGC | GTATTGGGCG | CTCTTCCGCT | TCCTCGCTCA | CTGACTCGCT |
| 4151 | GCGCTCGGTC | GTTCCGGCTG | GGCGAGCGGT | ATCAGCTCAC | TCAAAGGCGG |
| 4201 | TAATACGGTT | ATCCACAGAA | TCAGGGGATA | ACGCAGGAAA | GAACATGTGA |
| 4251 | GCAAAGGCC | AGCAAAAGGC | CAGGAACCGT | AAAAAGGCCG | CGTTGCTGGC |
| 4301 | GTTTTTCCAT | AGGCTCCGCC | CCCCTGACGA | GCATCACAAA | AATCGACGCT |
| 4351 | CAAGTCAGAG | GTGGCGAAAC | CCGACAGGAC | TATAAGATA | CCAGGCGTTT |
| 4401 | CCCCCTGGAA | GCTCCCTCGT | GCGCTCTCCT | GTTCCGACCC | TGCCGCTTAC |
| 4451 | CGGATACCTG | TCCGCCCTTC | TCCCTTCGGG | AAGCGTGGCG | CTTTCTCAAT |
| 4501 | GCTCACGCTG | TAGGTATCTC | AGTTCGGTGT | AGGTCGTTCT | CTCCAAGCTG |
| 4551 | GGCTGTGTGC | ACGAACCCCC | CGTTACGCCC | GACCGCTGCG | CCTTATCCGG |
| 4601 | TAACATATCGT | CTTGAGTCCA | ACCCGGTAAG | ACACGACTTA | TCGCCACTGG |
| 4651 | CAGCAGCCAC | TGGTAACAGG | ATTAGCAGAG | CGAGGTATGT | AGGCGGTGCT |
| 4701 | ACAGAGTTCT | TGAAGTGGTG | GCCTAACTAC | GGCTACACTA | GAAGGACAGT |
| 4751 | ATTTGGTATC | TGCGCTCTGC | TGAAGCCAGT | TACCTTCGGA | AAAAGAGTTG |
| 4801 | GTAGCTCTTG | ATCCGGCAAA | CAAAACCCAG | CTGGTAGCGG | TGTTTTTTTT |
| 4851 | GTTTGCAAGC | AGCAGATTAC | GCGCAGAAAA | AAAGGATCTC | AGGAAGATCC |
| 4901 | TTTGATCTTT | TCTACGGGGT | CTGACGCTCA | GTGGAACGAA | AACTCACGTT |
| 4951 | AAGGGATTTT | GGTCAATGAA | TTATCAAAAA | GGATCTTCAC | CTAGATCCTT |
| 5001 | TTAAATTAAA | AGTAAAGTTT | TAAATCAATC | TAAAGTATAT | ATGAGTAAAC |
| 5051 | TTGGTCTGAC | AGTTACCAAT | CGTTAATCAG | TGAGGCACCT | ATCTCAGCGA |
| 5101 | TCTGTCTAIT | TCGTTTATCC | ATAGTTGCCT | GACTCCCCGT | CTGTGAGATA |
| 5151 | ACTACGATAC | GGGAGGGCTT | ACCATCTGGC | CCCAGTGCTG | CAATGATACC |
| 5201 | CGGAGACCCA | CGCTCACCGG | CTCCAGATT | ATCAGCAATA | AACCAGCCAG |
| 5251 | CCGGAAGGGC | CGAGCGCAGA | AGTGGTCTGT | CAACTTTATC | CGCCTCCATC |
| 5301 | CAGTCTATTA | ATTGTTGCCG | GGAAAGCTAGA | TGAAGTAGTT | CGCCAGTTAA |
| 5351 | TAGTTTGCGC | AACGTTGTTG | CCATTGCTAC | AGGCATCGTG | GTGTCACGCT |
| 5401 | CGTCGTTTGG | TATGGCTTCA | TTCAGCTCCG | GTTCCCAACG | ATCAAGGCGA |
| 5451 | GTTACATGAT | CCCCCATGTT | GTGCAAAAAA | GCGGTTAGCT | CCTTCGGTCC |
| 5501 | TCCGATCGTT | GTCAGAAGTA | AGTTGGCCGC | AGTGTTATCA | CTCATGGTTA |
| 5551 | TGGCAGCACT | GCATAATTCT | CTTACTGTCA | TGCCATCCGT | AGATGCTTTT |
| 5601 | TCTGTGACTG | GTGAGTACTC | AACCAAGTCA | TTCTGAGAAT | AGTGTATGCG |
| 5651 | GCGACCGAGT | TGCTCTTGCC | CGGCGTCAAT | ACGGGATAAT | ACCGCGCCAC |
| 5701 | ATAGCAGAAC | TTTAAAGGTG | CTCATCATTT | GAAAACGTTT | TTCCGGGGCGA |
| 5751 | AAACTCTCAA | GATGCTTACC | CGTGTGAGA | TCCAGTTCGA | TGTAACCCAC |
| 5801 | TCGTGCACCC | AACTGATCTT | CAGCATCTTT | TACTTTCACC | AGCGTTTCTG |
| 5851 | GGTGAGCAAA | AACAGGAAGG | CAAAATGCCG | CAAAAAAGGG | AATAAGGGCG |
| 5901 | ACACGGAAAT | GTTGAATACT | CATACTCTTC | CTTTTTCAAT | ATTATTGAAG |
| 5951 | CATTTATCAG | GGTTATTGTC | TCATGAGCGG | ATACATATTT | GAATGTATTT |
| 6001 | AGAAAAATAA | ACAAATAGGG | GTTCCGCGCA | CATTTCCCCG | AAAAGTGCCA |
| 6051 | CCTGACGCTC | AAGAAACCAT | TATTATCATG | ACATTAACCT | ATAAAAAATAG |
| 6101 | GCGTATCACG | AGGCCCTTTC | GTCTCGCGCG | TTTCGGTGAT | GACGGTGAAA |
| 6151 | ACCTCTGACA | CATGACAGCTC | CCGGAGACGG | TCACAGCTTG | TCTGTAAGCG |
| 6201 | GATGCCGGGA | CGAGACAAGC | CCGTACAGGG | GCGTCAGCGG | GTGTTGGCGG |
| 6251 | GTGTCGGGGC | TGGCTTAACT | ATGCGGCATC | ASAGCAGATT | GTACTGAGAG |
| 6301 | TGCACCATAT | CGCGTGTGAA | ATACCCGACA | GATGCGTAAG | GAGAAAAATAC |
| 6351 | CGCATCAGGC | CCCATTCGCC | ATTCAGGCTG | CGCAACTGTT | GGGAAGGGCG |
| 6401 | ATCGGTGCGG | GCCTCTTTCG | TATTACGCCA | GCTGGCGAAA | GGGGGATGTG |
| 6451 | | | | | |

Fig. 5

- 12/35 -

```
6601 CTGGCTCGCA AAACATGTTT CCTTGGCTGC TTTCCACTTC CCCTTGTGCT
6651 TTGTTTACTT GTGTCAGCTG GTTGGCTCCC TAGGTATGAG CTCATGCTTG
6701 GCTGGCAGCC ATCCAGTTTT AGCCAGCTCT GCTT1GTTTA CTTGTGTCAG
6751 CTCGTTGGCT CCCTAGGTAT GAGCTCATGC TTGGCTGGCA GCCATCCAGT
6801 TTTAGCCAGC TCCTCCCTAC CTTCCCTTTT TTTTATATAT ACAGGAGGCC
6851 GAGGCCGCCT CCGCCTCCAA GCTTACTCAG AAGTAGTAAG GGCCTGGAGG
6901 CTTTTTAGGA GGCCAGGGAA ATTCCCTTGT TTTTCCCTTT TTTGCAGTAA
6951 TTTTTTGCTG CAAAAAGCTA A
```

Fig. 5

pD12JCVFshort-hCNTF

Length: 7558

1 GCTAGCGATT TAGGTGACAC TATAGAATCt cgacnngTCA CCCCTAGAGT
 51 CGAGCTGTGA CCGTCCTTAC AATGAAATGC ANCTGGGTTA TCTTCTTCCT
 101 GATGGCAGGG GTTACAGGTA AGGGGCTCCC AAGTCCCAA CTTGAGGGTC
 151 CATAAACTCT GTGACAGTGG CAATCACTTT GCCTTTCTTT CTACAGGGGT
 201 GAATTCGGCT TTCACAGAGC ATTCACCGCT GACCCCTCAC CGTCGGGACC
 251 TCTGTAGCCG CTCTATCTGG CTAGCAAGGA AGATTGTTT AGACCTTGAC
 301 TGCTCTTACG GAATCCTATG TAAGTTGCCT ATTTTGCTGT TATCTGTTTT
 351 CCCTTCATCT TTTTGTATCC AGCAACTTAC CATCAAGCAT CAGCTCCATT
 401 ACCAATTGTG AAAGCTCTAA TCATATAGTC ATTCATATAG GTTATTTGAC
 451 ATGGGCCCTT CCCTTGAGGA AACCCTATGT ACTTTATTTT CTTCCTCTGG
 501 GCTGTTTAGG AGATGAAGTT ACTTGAATGA GAAAATATAT ATGGAGTTCT
 551 AGAAAGGATT GGTTTATATG TCTTGGAGGC TATTTCAAAA TTTATTTGGC
 601 CATATATTCT GAATACTACC TAGAACAGAT TAGCCATGGG CCCTTTGGGT
 651 TTTTCATAAG CCATTGTTCT GAANTTTTTT AGCTTTGTAA ATGAAAGTT
 701 TATGGGATAG GAAGAGTNCT ATGAACGTGG GAGGAATTTG TAAATCCTAC
 751 CAATTNTNC TATATAGCAT TAGCCCCCAC CTTTANTAT TCTGCATCAA
 801 AAGTAAGATT GTGTCTAAAG AGAAAGGTNA GCTATCAAAA GGACTCCTAT
 851 AANATTCNTT GGAACTTNT GGAANTGTCA AATTNTTTTG AGCTAATTNT
 901 TGGAGTTCCA AANTTTGTCT TTTMACAGTN AAGGGGGANC CCCATTCAAA
 951 TTTNCCCCC TTTNGANAAT GCTTGGGGGA AAAAACCTNC CAACCCNTT
 1001 GTGGGANGAA GTTTTTTAA NNTTTTAAAG CTNGNGAAA CMGGNTTTTA
 1051 ATTTTTTGGG NCNANCGCCT NTCCCCGTA CCAGGAAAAT CAGGACCTNT
 1101 TTTTGGGGNN GNGCNCCNAC NGGGGGGNA AANGGGAAAT TTCNTCANAA
 1151 AAAATCTTTT CCGnnnnnnng tgaagcatca gggcctgaac aagaacatca
 1201 acctggactc tgcggatggg atgccagtgg caagcactga tcagtggagt
 1251 gagctg ccg aggcagagcg actccaagag aaccttcaag cttatcgtac

Fig. 6

1301 cttccatggt ttgttggcca ggctcttaga aga cagcag gtgcatttta
1351 ccccaa cga aggtgacttc catcaagcta tacataccct tcttctccaa
1401 gtcgctgcct ttgcat cca gatagaggag ttaatgat c tcctggaata
1451 caag tcccc cgcaatgagg ctgatgggat gcctattaat gttgg gatg
1501 gtgggtctctt tgagaagaag ctgtggggcc taaagggtgct gcaggagctt
1551 tcacagtggg cagtaaggtc catccatgac ctctgtttca tttcttctca
1601 tcagactggg atcccagcac gtgggagcca ttatattgct aacaacaaga
1651 aaatgtagnn nnnngggcct GCGCCGTCCT TCCCGACGTT AAAGGGATGA
1701 AACCACAAGA CTTACCTTCG CTCGGAAGTA AAACGACAAA CACACACAGT
1751 TTTGCCCCGT TTCTAGAGAA ATGGGACGTC TCGGCACGAA ACGCGCCGTC
1801 GCTTGAGGAG GACTTGTACA AACACGATCT ATGCAGGTTT CCCCAACTGA
1851 CACAAACCGT GCAACTTGAA ACTCCGCCTG GTCTTTCCAG GTCTAGAGGG
1901 GTAACATTTT GTA CTGTGTGT TGA CTCCAG CTGATCCAC TAGCGAGTGT
1951 TAGTAGCGGT ACTGCTGTCT CGTAGCGGAG CATGTTGGCC GTGGGAACAC
2001 CTCCTTG GTA ACAAGGACCC ACGGGGCGGA AAGCCATGTC CTAACGGACC
2051 CAACATGTGT GCAACCCAG CACGGCAGCT TTA CTGTGAA ACCCACTTCA
2101 AGGTGACATT GATACTG GTA CTCAACACT GGTGACAGGC TAAGGATGCC
2151 CTT CAGGTAC CCGAGGTAA CAAGCGACAC TCGGGATCTG AGAAGGGGAC
2201 TGGGACTTCT TTAAAGTGCC CAGTTTAAA AGCTTCTACG CCTGAATAGG
2251 TGACCGGAGG CCGGCACCTT TCCTTTTATA ACCACTGAAC ACATGGAAGA
2301 CGCCAAAAC ATAAAGAAAG GCCCGGCGCC ATTCTATCCT CTAGAGGATG
2351 GAACCGCTGG AGAGCAACTG CATAAGGCTA TGAAGAGATA CGCCCTGGTT
2401 CCTGGAACAA TTGCTTTTAC AGATGCACAT ATCGAGGTGA ACATCACGTA
2451 CGCGGAATAC TTCGAAATGT CCGTTCGGTT GGCAGAAGCT ATGAAACGAT
2501 ATGGGCTGAA TACAAATCAC AGAATCGTCG TATGCAGTGA AAACCTCTCT
2551 CAATTCITTA TGCCGGTGTT GGGCGCGTTA TTTATCGGAG TTCCAGTTGC
2601 GCCCGCGAAC GACATTTATA ATGAACGTGA ATTGCTCAAC AGTATGAACA
2651 TTTCGCAGCC TACCGTAGTG TTTGTTTCCA AAAAGGGGTT GCAAAAATT

Fig. 6

2701 TTGAACGTGC AAAAAAATT ACCAATAATC CAGAAAATTA TTATCATGGA
2751 TTCTAAAACG GATTACCAGG GATTTCAGTC GATGTACACG TTCGTCACAT
2801 CTCATCTACC TCCCGGTTTT AATGAATAAG ATTTTGTACC AGAGTCCTTT
2851 GATCGTGACA AAACAATTGC ACTGATAATG AATTCCTCTG GATCTACTGG
2901 GTTACCTAAG GGTGTGGCCC TTCGCGATAG AACTGCCTGC GTCAGATTCT
2951 CGCATGCCAG AGATCCTATT TTTGGCAATC AAATCATTCC GGATACTGCG
3001 ATTTTAAGTG TTGTTCCATT CCATCACGGT TTTGGAATGT TACTACACT
3051 CGGATATTTG ATATGTGGAT TTCGAGTCGT CTTAATGTAT AGATTTGAAG
3101 AAGAGCTGTT TTTACGATCC CTTCAGGATT ACAAAATTCA AAGTGCCTTG
3151 CTAGTACCAA CCCTATTTTC ATTCTTCGCC AAAAGCACTC TGATTGACAA
3201 ATACGATTTA TCTAATTTAC ACGAAATTGC TTCTGGGGGC GCACCTCTTT
3251 CGAAAGAAGT CGGGGAAGCG GTTGCAAAAC GCTTCCATCT TCCAGGGATA
3301 CGACAAGGAT ATGGGCTCAC TGAGACTACA TCAGCTATTC TGATTACACC
3351 CGAGGGGGAT GATAAACCGG GCGCGGTCGG TAAAGTTGTT CCATTTTTTG
3401 AAGCGAAGGT TGTGGATCTG GATACCGGGA AAACGCTGGG CGTTAATCAG
3451 AGAGGCGAAT TATGTGTCAG AGGACCTATG ATTATGTCCG GTTATGTAAA
3501 CAATCCGGAA GCGACCAACG CCTTGATTGA CAAGGATGGA TGGCTACATT
3551 CTGGAGACAT AGCTTACTGG GACGAAGACG AACACTTCTT CATAGTTGAC
3601 CGCTTGAAGT CTTTAATTAA ATACAAAGGA TATCAGGTGG CCCCCGCTGA
3651 ATTGGAATCG ATATTGTTAC AACACCCCAA CATCTTCGAC GCGGGCGTGG
3701 CAGGTCTTCC CGACGATGAC GCCGGTGAAC TTCCGCGCGC CGTTGTGTGT
3751 TTGGAGCACG GAAAGACGAT GACCGAAAAA GAGATCGTGG ATTACGTCCG
3801 CAGTCAAGTA ACAACGCGA AAAAGTTGCG CGGAGGAGTT GTGTTTGTGG
3851 ACGAAGTACC GAAAGGTCTT ACCGGA AAAC TCGACGCAAG AAAAATCAGA
3901 GAGATCCTCA TAAAGGCCAA GAAGGGCGGA AAGTCCAAAT TGTA AAATGT
3951 AACTGTATTC AGCGATGACG AAATTCCTAG CTATTGTAAT GACTCTAGAG
4001 GATCTTTGTG AAGGAACCTT ACTTCTGTGG TGTGACATAA TTGGACAAAC
4051 TACCTACAGA GATTAAAGC TCTAAGGTAA ATATAAAATT TTTAAGTGTA

Fig. 6

4101 TAATGTGTTA AACTACTGAT TCTAATGTGT TGTGTATTTT AGATTCCAAC
4151 CTATGGAACT GATGAATGGG AGCAGTGGTG GAATGCCTTT AATGAGGAAA
4201 ACCTGTTTTG CTCAGAAGAA ATGCCATCTA GTGATGATGA GGCTACTGCT
4251 GACTCTCAAC ATTCTACTCC TCCAAAAAAG AAGAGAAAGG TAGAAGACCC
4301 CAAGGACTTT CCTTCAGAAT TGCTAAGTTT TTTGAGTCAT GCTGTGTTTA
4351 GTAATAGAAC TCTTGCTTGC TTTGCTATTT ACACCACAAA GGAAAAAGCT
4401 GCACTGCTAT ACAAGAAAAT TATGGAAAAA TATTCTGTAA CCTTTATAAG
4451 TAGGCATAAC AGTTATAATC ATAACATACT GTTTTTTCTT ACTCCACACA
4501 GGCATAGAGT GTCTGCTATT AATAACTATG CTCAAAAATT GTGTACCTTT
4551 AGCTTTTAA TTTGTAAAGG GGTTAATAAG GAATATTTGA TGTATAGTGC
4601 CTTGACTAGA GATCATAATC AGCCATACCA CATTTGTAGA GGTTTTACTT
4651 GCTTTAAAAA ACCTCCCACA CCTCCCCCTG AACCTGAAAC ATAAATGAA
4701 TGCAATTGTT GTTGTTAACT TGTTTATTGC AGCTTATAAT GGTACAAAT
4751 AAGCAATAG CATCACAAAT TTCACAAATA AAGCATTTTT TTCACTGCAT
4801 TCTAGTTGTG GTTTGTCCAA ACTCATCAAT GTATCTTATC ATGCTCTGGAT
4851 CCCCGGGTCC CTATAGTGAG TCGTATTAGC TTGGCGTAAT CATGGTCATA
4901 GCTGTTTCCT GTGTGAAATT GTTATCCGCT CACAATTCCA CACAACATAC
4951 GAGCCGGAAG CATAAAGTGT AAAGCCTGGG GTGCCIAATG AGTGAGCTAA
5001 CTCACATTAA TTGCGTTGCG CTCACTGCCC GCTTTCAGT CGGGAAACCT
5051 GTCGTGCCAG CTGCATTAAAT GAATCGGCCA ACGCGCGGGG AGAGGCGGTT
5101 TGCGTATTGG GCGCTCTTCC GCTTCTCGC TCACTGACTC GCTGCGCTCG
5151 GTCGTTCCGC TCGGCGGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG
5201 GTTATCCACA GAATCAGGGG ATAACGCAGG AAAGAACATG TGAGCAAAAG
5251 GCCAGCAAAA GGCCAGGAAC CGTAAAAAGG CCGCGTTGCT GCGGTTTTTC
5301 CATAGGCTCC GCCCCCTGA CGAGCATCAC AAAAATCGAC GCTCAAGTCA
5351 GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG
5401 GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC
5451 CTGTCCGCCT TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC AATGCTCACG

Fig. 6

5501 CTGTAGGTAT CTCAGTTCGG TGTAGGTGGT TCGCTCCAAG CTGGGCTGTG
5551 TGCACGAACC CCCCGTTGAG CCGACCGCT GCGCCTTATC CGGTAACAT
5601 CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC TGGCAGCAGC
5651 CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT
5701 TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGGAC AGTATTTGGT
5751 ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAGAG TTGGTAGCTC
5801 TTGATCCGGC AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA
5851 AGCAGCAGAT TACGCGCAGA AAAAAAGGAT CTCAAGAAGA TCCTTTGATC
5901 TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT
5951 TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTMTTAAATT
6001 AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
6051 GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT
6101 ATTTGCTTCA TCCATAGTTG CCTGACTCCC CGTCGTGTAG ATAACCTACGA
6151 TACGGGAGGG CTTACCATCT GGCCCCAGTG CTGCAATGAT ACCGCGAGAC
6201 CCAAGCTCAC CGGCTCCAGA TTTATCAGCA ATAAACCAGC CAGCCGGAAG
6251 GCGCGAGCGC AGAAGTGGTC CTGCAACTTT ATCCGCCTCC ATCCAGTCTA
6301 TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG
6351 CGCAACGTTG TTGCCATTGC TACAGGCATC GTGGTGTCAC GCTCGTCTTT
6401 TGGTATGGCT TCATTACGCT CCGGTTCCCA ACGATCAAGG CGAGTTACAT
6451 GATCCCCCAT GTTGTGCAAA AAAGCGGTTA GCTCCTTCGG TCCTCCGATC
6501 GTTGTGAGAA GTAAGTTGGC CGCAGTGTTA TCACTCATGG TTATGGCAGC
6551 ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC TTTTCTGTGA
6601 CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT GCGGCGACCG
6651 AGTTGCTCTT GCGCGGCGTC AATACGGGAT AATACGCGC CACATAGCAG
6701 AACTTTAAAA GTGCTCATCA TTGGAAAACG TTCTTCGGGG CGAAACTCT
6751 CAAGGATCTT ACCGCTGTTG AGATCCAGTT CGATGTAACC CACTCGTGCA
6801 CCCAAGTAT CTTCAGCATC TTTTACTTTC ACCAGCGTTT CTGGGTGAGC
6851 AAAAACAGGA AGGCAAAATG CCGCAAAAAA GGAATAAGG GCGACACGGA

Fig. 6

6901 AATGTTGAAT ACTCATACTC TTCCTTTTTC AATATTATTG AAGCATTIAT
6951 CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA
7001 TAAACAAATA GGGGTTCCGC GCACATTTCC CCGAAAAGTG CCACCTGACG
7051 TCTAAGAAAC CATTATTATC ATGACATTAA CCTATAAAAA TAGGCGTATC
7101 ACGAGGCCCT TTCGTCTCGC GCCTTTCGGT GATGACGGTG AAAACCTCTG
7151 ACACATGCAG CTCCCGGAGA CGGTCACAGC TTGTCTGTAA GCGGATGCCG
7201 GGAGCAGACA AGCCCGTCAG GCGCGTCAG CGGGTGTTGG CCGGTGTCGG
7251 GGCTGGCTTA ACTATGCGGC ATCAGAGCAG ATTGTACTGA GAGTGCACCA
7301 TATGCGGTGT GAAATACCGC ACAGATGCGT AAGGAGAAAA TACCGCATCA
7351 GCGGCCATTTC GCCATTGAGG CTGCGCAACT GTTGGGAAGG GCGATOGGTG
7401 CCGGCCTCTT CGCTATTACG CCAGCTGGCG AAAGGGGGAT GTGCTGCAAG
7451 GCGATTAAGT TGGGTAACGC CAGGGTTTTC CCAATCACGA CGTTGTAAAA
7501 CGACGGCCAG TGAATTTGGA CCTGCAGtcg acttttttta tatatacagg
7551 aggcagag

Fig. 6

- 19/35 -

JCVPshort-hgdnf Length: 6565 June 8, 1999 16:57 Type: N Check:

```

1   GCTAGCGATT TAGGTGACAC TATAGAATAG ATCCCCATGA AGTTATGGGA
51  TGTCGTGGCT GTCTGCCTGG TGCTGCTCCA CACCGCGTCC GCCTTCCCGC
101 TGCCCCGCCG TAAGAGGCCT CCGAGGCGC CCGCCGAAGA CCGCTCCCTC
151 GGCCGCCGCC GCGCGCCCTT CGCGCTGAGC AGTGACTCAA ATATGCCAGA
201 GGATTATCCT GATCAGTTCG ATGATGTCAT GGATTTTATT CAAGCCACCA
251 TTTAAAGACT GAAAAGGTCA CCAGATAAAC AAATGGCAGT GCTTCCTAGA
301 AGAGAGCGGA ATCGGCAGGC TGCAGCTGCC AACCCAGAGA ATTCCAGAGG
351 AAAAGGTCCG AGAGGCCAGA GGGGCAAAAA CCGGGGTGTG GTCTTAACTG
401 CAATACATTT AAATGTCACT GACTTGGGTC TGGGCTATGA AACCAGGAG
451 GAACTGATTT TTAGGTACTG CAGCGGCTCT TGCGATGCAG CTGAGACAAC
501 GTACGACAAA ATATTGAAAA ACTTATCCAG AAATAGAAGG CTGGTGAATG
551 ACAAAGTAGG SCAGGCATGT TGCAGACCCA TCGCCTTTGA TGATGACCTG
601 TCGTTTTTAG ATGATAACCT GGTTTTACCAT ATTCTAAGAA AGCATTCCGC
651 TAAAAGGTGT GGATGTATCT GACTGGTGCG CCGTCTTTCC CGACGTTAAA
701 GGGATGAAAC CACAAGACTT ACCTTCGCTC GGAAGTAAAA CGACAAACAC
751 ACACAGTTT GCCCGTTTTT ATGAGAAATG GGACGTCTGC GCACGAAACG
801 CGCCGTGCTT TGAGGAGGAC TTGTACAAAC ACGATCTATG CAGGTTTCCC
851 CAACTGACAC AAACCGTGCA ACTTGAAACT CCGCCTGGTC TTCCAGGTC
901 TAGAGGGGTA ACATTTTGTA CTGTGTTTGA CTCCACGCTC GATCCACTAG
951 CGAGTGTTAG TAGCGGTACT GCTGTCTCGT AGCGGAGCAT GTTGGCCGTG
1001 GGAACACCTC CTTGGTAACA AGGACCCACG GGGCCGAAG CCATGTCCTA
1051 ACGGACCCAA CATGTGTGCA CCCCAGCAC GGCAGCTTTA CTGTGAACCC
1101 CACTTCAAGG TGACATTGAT ACTGGTACTC AAACACTGGT GACAGGGTAA
1151 GGATGCCCTT CAGGTACCCC GAGGTAACAA GCGACACTCG GGATCTGAGA
1201 AGGGGACTGG GACTTCTTTA AAGTGCCAG TTTAAAAGC TTCTACGCCT
1251 GAATAGGTGA CCGGAGGCCG GCACCTTTCC TTTTATAACC ACTGAACACA
1301 TGGGAAGACG CAAAACATA AAGAAAGGCC CGGCGCCATT CTATCCTCTA
1351 SAGGATGGAA CCGCTGGAGA GCAACTGCAT AAGGCTATGA AGAGATACGC
1401 CCTGGTTCCT GGAACAATTG CTTTTACAGA TGCACATATC GAGGTGAACA
1451 TCACGTACGC GGAATACTTC GAAATGTCCG TTCGGITGGC AGAAGCTATG
1501 AAACGATATG GGCTGAATAC AAATCACAGA ATCCTCGTAT GCAGTGAAAA
1551 CTCTCTTCAA TTCTTTATGC CGGTGTTGGG CGCGTTATTT ATCGGAGTTG
1601 CAGTTGCGCC CGCGAACGAC ATTTATAATG AACGTGAATT GCTCAACAGT
1651 ATGAACATTT CGCAGCCTAC CGTAGTGTTT GTTTCCAAAA AGGGGTGCA
1701 AAAAATTTTG AACGTGCAAA AAAAATTACC AATAATCCAG AAAATTATTA
1751 TCATGGATTG TAAAACGGAT TACCAGGGAT TTCAGTCGAT GTACACGTTT
1801 GTCACATCTC ATCTACCTCC CGGTTTTAAT GAATACGATT TTGTACCAGA
1851 GTCCTTTGAT CGTGACAAAA CAATTGCACT GATAATGAAT TCCTCTGGAT
1901 CTACTGGGTT ACCTAAGGGT GTGGCCCTTC CGCATAGAAC TGCCTGCGTC
1951 AGATTCTCGC ATGCCAGAGA TCCTATTTTT GGAATCAAA TCATTCCGGA
2001 TACTGCGATT TTAAGTGTTG TTCCATTCCA TCACGGTTTT GGAATGTTTA
2051 CTACACTCGG ATATTTGATA TGTGGATTTT GAGTCGTCTT AATGTATAGA
2101 TTTGAAGAAG AGCTGTTTTT ACGATCCCTT CAGGATTACA AAATTCAAAG
2151 TGCGTTGCTA GTACCAACCC TATTTTCATT CTTGCGCAAA AGCACTCTGA
2201 TTGACAAATA CGATTTATCT AATTACACG AAATTGCTTC TGGGGGCGCA
2251 CCTCTTTTGA AAGAAGTCGG GGAAGCGGTT GCAAAACGCT TCCATCTTCC
2301 AGGGATACCA CAAGGATATG GGCTCACTGA GACTACATCA GCTATTCTGA
2351 TTACACCCGA CGGGGATGAT AAACCGGGCG CGGTGCGTAA AGTTGTTCCA
2401 TTTTTTGAAG CGAAGGTTGT GGATCTGGAT ACCGGGAAAA CGCTGGGCGT
2451 TAATCAGAGA GGCGAATTAT GTGTCAGAGG ACCTATGATT ATGTCCGGTT
2501 ATGTAAACAA TCCGGAAGCG ACCAACGCCT TGATTGACAA GGATGGATGG
2551 CTACATTCTG GAGACATAGC TTAAGTCTT TAATTAAATA CAAAGGATAT CAGGTGGCCC
2601 AGTTGACCGC TTGAAGTCTT TAATTAAATA CAAAGGATAT CAGGTGGCCC
2651 CCGCTGAATT GGAATCGATA TTGTTACAAC ACCCAACAT CTTGACGCG
2701 GCGTGCGCAG GTCTTCCCGA CGATGACGCC GGTGAACCTC CCGCCGCCGT
2751 TGTGTTTTTG GAGCACGGAA AGACGATGAC GGAAAAAGAG ATCGTGGATT
2801 ACGTCGCCAG TCAAGTAACA ACCGCGAAAA AGTTGCGCGG AGGAGTTGTG
2851 TTTGTGACG AAGTACCGAA AGGTCTTACC GGAAACTCG ACGCAAGAAA
2901 AATCAGAGAG ATCCTCATAA AGGCCAAGAA GGGCGGAAAG TCCAAATTGT
2951 AAAATGTAAC TGTATTGAGC GATGACGAAA TTCTTAGCTA TTGTAATGAC
3001 TCTAGAGGAT CTTTGTGAAG GAACCTTACT TCTGTGGTGT GACATAATTG
3051 CACAACTAC CTACAGAGAT TTAAAGCTCT AAGGTAAATA TAAAATTTTT
3101 AAGTGATATA TGTGTTAAAC TACTGATTCT AATTGTTTTG GTATTTTAGA
3151 TTCCAACCTA TGGAAGTGT GAATGGGAGC AGTGGTGGAA TGCCTTTAAT

```

Fig. 7

- 20/35 -

```

3201 GAGGAAAACC TGTTTTGCTC AGAAGAAATG CCATCTAGTG ATGATGAGGC
3251 TACTGCTGAC TCTCAACATT CTACTCCTCC AAAAAAGAAG AGAAAGGTAG
3301 AAQACCCCAA GGACTTTTCT TCAGAATTGC TAAGTTTTTT GAGTCATGCT
3351 GTGTTTAGTA ATAGAACTCT TGCTTGCTTT GCTATTTACA CCACAAAGGA
3401 AAAAGCTGCA CTGCTATACA AGAAAATTAT GGAAAAATAT TCTGTAACCT
3451 TTATAAGTAG GCATAACAGT TATAATCATA ACATACTGTT TTTTCTTACT
3501 CCACACAGGC ATAGAGTGTC TGCTATTAAT AACTATGCTC AAAAATTGTG
3551 TACCTTTAGC TTTTAAATTT GTAAAGGGGT TAATAAGGAA TATTGATGT
3601 ATAGTGCTT GACTAGAGAT CATAATCAGC CATACCACAT TTGTAGAGGT
3651 TTTACTTGCT TTA AAAAACC TCCACACCT CCCCCTGAAC CTGAAACATA
3701 AAATGAATGC AATTGTTGTT GTTAACCTGT TTATGTCAGC TTATAATGGT
3751 TACAAATAAA CCAATAGCAT CACAAATTTT ACAAATAAAG CATTTTTTTT
3801 ACTGCATTCT AGTTGTGGTT TGTCCAACT CATCAATGTA TCTTATCATG
3851 TCTGGATCCC CGGGTCCCTA TAGTGAGTCG TATTAGCTTG GCGTAATCAT
3901 GGTACATAGC GTTCTCTGTG TGAAATTGTT ATCCGCTCAC AATTCCACAC
3951 AACATACGAG CCGGAAGCAT AAAGTGTAAG GCCTGGGGTG CCTAATGAGT
4001 GAGCTAACTC ACATTAATTG CGTTGCGCTC ACTGCCCGCT TTCCAGTCGG
4051 GAAACCTGTC GTGCCAGCTG CATTAATGAA TCGGCCAACG CGCGGGGAGA
4101 GCGGGTTTGC GTATTGGGCG CTCTTCCGCT TCTCTGCTCA CTGACTCGCT
4151 GCGCTCGGTC GTTCGGCTGC GGCGAGCGGT ATCAGCTCAC TCAAAGCGCG
4201 TAATACGGTT ATCCACAGAA TCAGGGGATA ACGCAGGAAA GAACATGTGA
4251 GCAAAAGGCC AGCAAAAGGC CAGGAACCGT AAAAAAGGCC CGTTGCTGGC
4301 GTTTTTCCAT AGGCTCCGCC CCCCTGACGA GCATCACAAA AATCGACGCT
4351 CAAGTCAGAG GTGGCGAAG CCGACAGGAC TATAAAGATA CCAGGCGTTT
4401 CCCCCTGGAA GCTCCCTCGT GCTCCTCTCT GTTCCGACCC TGCCGCTTAC
4451 CGGATACCTG TCCGCCCTTC TCCCTTCGGG AAGCGTGGCG CTTTCTCAAT
4501 GCTCACGCTG TAGGTATCTC AGTTCGGTGT AGGTCGTTCT CTCCAAGCTG
4551 GGTGTGTGTC ACGAACCCCT CGTTCAGCCC GACCGCTGCG CCTTATCCGG
4601 TAATATCTGT CTTGAGTCCA ACCCGGTAAG ACACGACTTA TCGCCACTGG
4651 CAGCAGCCAC TGGTAACAGG ATTAGCAGAG CGAGGTATGT AGGCGGTGCT
4701 ACAGAGTTCT TGAAGTGGTG GCCTAACTAC GGCTACACTA GAAGGACAGT
4751 ATTTGGTATC TGCGCTCTGC TGAAGCCAGT TACCTTCGGA AAAAGAGTTG
4801 GTAGCTCTTG ATCCGGCAAA CAAACCACCG CTGGTAGCGG TGGTTTTTTT
4851 GTTTGCAAGC AGCAGATTAC GCGCAGAAAA AAAGGATCTC AAGAAGATCC
4901 TTTGATCTTT TCTACGGGGT CTGACGCTCA GTGGAACGAA AACTACGTT
4951 AAGGGATTTT GGTCAATGAGA TTATCAAAAA GGATCTTCAC CTAGATCCTT
5001 TTAAATTAAG AATGAAGTTT TAAATCAATC TAAAGTATAT ATGAGTAAAC
5051 TTGGTCTGAC AGTTACCAAT GCTTAATCAG TGAGGCACCT ATCTCAGCGA
5101 TCTGTCTATT TCGTTCATCC ATAGTTGCCT GACTCCCCGT CGTGTAGATA
5151 ACTACGATAC GGGAGGGCTT ACCATCTGGC CCCAGTGCTG CAATGATACC
5201 GCGAGACCCA CGCTCACCGG CTCCAGATTT ATCAGCAATA AACCAGCCAG
5251 CCGGAAGGGC CGAGCGCAGA AGTGGTCTCT CAACTTTATC CGCCTCCATC
5301 CAGTCTATTA ATTGTTGCCG GGAAGCTAGA GTAAGTAGTT CGCCAGTTAA
5351 TAGTTTGCGC AACGTTGTTG CCATTGCTAC AGGCATCGTG GTGTCACGCT
5401 CGTCGTTTGG TATGGCTTCA TTCAGCTCCG GTTCCCAACG ATCAAGGCGA
5451 GTTACATGAT CCCCATGTT GTGCAAAAAA GCGGTTAGCT CCTTCGGTCC
5501 TCCGATCGTT GTCAGAAGTA AGTTGGCCGC AGTGTTATCA CTCATGGTTA
5551 TGGCAGCACT GCATAATTCT CTTACTGTCA TGCCATCCGT AAGATGCTTT
5601 TCTGTGACTG GTGAGTACTC AACCAGTCA TTCTGAGAAT AGTGTATGCG
5651 GCGACCGAGT TGCTCTTGCC CGGCGTCAAT ACGGGATAAT ACCGCGCCAC
5701 ATAGCAGAAC TTTAAAAGTG CTCATCATTT GAAAACGTTT TTCGGGGCGA
5751 AAATCTCAA GGATCTTACC GCTGTTGAGA TCCAGTTCGA TGTAAACCCAC
5801 TCGTGCACCC AACTGATCTT CAGCATCTTT TACTTTCACC AGCGTTTCTG
5851 GGTGAGCAAA AACAGGAAGG CAAAATGCCG CAAAAAGGGG AATAAGGGCG
5901 ACACGGAAAT GTTGAATACT CATACTCTTC CTTTTTCAAT ATTATTGAAG
5951 CATTTATCAG GGTATTGTCT TCATGAGCGG ATACATATTT GAATGTATTT
6001 AGAAAAATAA ACAAATAGGG GTTCCGCGCA CATTTCCCGG AAAAGTGCCA
6051 CCTGACGTCT AAGAAACCAT TATTATCATG ACATTAACCT ATAAAAATAG
6101 GCGTATCAGC AGGCCCTTTC GTCTCGCGCG TTTCGGTGAT GACGGTGAAA
6151 AUCTCTGACA CATGCAGCTC CCGGAGACGG TCACAGCTTG TCTGTAAGCG
6201 GATGCCGGGA GCAGACAAGC CGCTCAGGGC GCGTCAGCGG GTGTTGGCGG
6251 GTGTCGGGGC TGGCTTAACT ATGCGGCATC AGAGCAGATT GACTGAGAG
6301 TGCACCATAT GCGGTGTGAA ATACCGCACA GATCGGTAAG GAGAAAATAC
6351 CGCATCAGGC GCCATTCCGC ATTCAGGCTG CGCAACTGTT GGGAAAGGGCG
6401 ATCGGTGCGG GCTCTTTCGC TATTACGCCA GCTGGCGAAA GGGGATGTG
6451 CTGCAAGGCG ATTAAGTTGG GTAACGCCAG GGTTTTCCCA GTCACGAGT
6501 TGTA AACGA CGGCCAGTGA ATTTCCAGCT GCAGTcgact ttttttatat

```

Fig. 7

Printed: 19-10-2001

SPEC

99116533

- 21/35 -

6551 atacaggagc ccgag

Fig. 7

- 22/35 -

pRetroOFF-E6E7 Length: 7840 June 10, 1999 12:21 Type: N Check: 5234

```
1 TCGAGTTTAC CACTCCCTAT CAGTGATAGA GAAAAGTGAA AGTCGAGTTT
51 ACCACTCCCT ATCAGTGATA GAGAAAAGTG AAAGTCGAGT TTACCACTCC
101 CTATCAGTCA TAGAGAAAGT GAAAGTCGAG TTTACCACTC CCTATCAGTG
151 ATAGAGAAAA GTGAAAGTCG AGTTTACCAC TCCCTATCAG TGATAGAGAA
201 AAGTGAAAGT CGAGTTTACC ACICCCCTATC AGTGATAGAG AAAAGTGAAG
251 TCGAGTTTAC CACTCCCTAT CAGTGATAGA GAAAAGTGAA AGTCGAGCTC
301 GGTACCCGGG TCGAGTAGGC GTGTACGGTG GGAGGCCTAT ATAAGCAGAG
351 CTCGTTTAGT GAACCGTCAG ATCGCCTGGA GACGCCATCC ACGCTGTTTT
401 GACCTCCATA GAAGACACCG GGACCGATCC AGCCTgcggc cgcagatcta
451 attcaccggt tagtataaaa gcagacattt tatgcaccaa aagagaactg
501 caatgtttca ggaccacacag gagcgaccca gaaagttacc acagttatgc
551 acagagctgc aaacaactat acatgatata atattagaat gtgtgtactg
601 caagcaacag ttactgcgac gtgaggtata tgactttgct tttcgggatt
651 latgcatagt atatagagat gggaaatccat atgctgtatg tgataaatgt
701 ttaaagtttt attctaaaat tagtgagtat agacattatt gttatagttt
751 gtatggaaca acattagaac agcaatacaa caaacctgtg tgtgatttgt
801 taattaggtg tattaactgt caaaagccac tytgtcctga agaaaagcaa
851 agacatctgg acaaaaagca aagattccat aatataaggg gtcggtggac
901 cggctcgatgt atgtcttgtt gcagatcctc aagaacacgt agagaaaccc
951 agctgtaate atgcatggag atacacctac attgcatgaa tatatgtag
1001 atttgcaccc aqagacaact gatctctact gttatgagca attaaatgac
1051 agctcagagg aggaggatga aatagatggt ccagctggac aagcagaacc
1101 ggacagagcc cattacaata ttgtaacctt ttggtgcaag tgtgactcta
1151 cgettcggtt gtgcgtacaa agcacacacg tagacattcg tactttggaa
1201 gacctgttaa tgggcacact aggaattgtg tgccccatct gttctcagaa
1251 accataalct accatggctg atcctgcagg atcccCGGG AACAACAACA
1301 ATTGCATTCA TTTTATGTTT CAGGTTTCAGG GGGAGGTGTG GGAGGTTTTT
1351 TAAAGCAAGT AAAACCTCTA CAAATGTGGT ATGGCTGATT ATGATCCTGC
1401 AAGCCTCGTC GTCTGGCCGG ACCACGCTAT CTGTGCAAGG TCCCCGACG
1451 CGCGCTCCAT GAGCAGAGCG TCGCGCCCCC TACCCACCGT ACTCGTCAAT
1501 TCCAAGGGCA TCGGTAAACA GAGCGCCGTA GGGGGCGGAG TCGTGGGGGG
1551 TAAATCCCGG ACCCGGGGAA TCCCGTCCC CCAACATGTC CAGATCGAAA
1601 TCGTCTAGCG CGTCGGCATG CGCCATCGCC ACGTCCCTGC CGTATAAGTG
1651 GAGCTCGTCC CCCAGGCTGA CATCGGTCGG GGGGGCCGTC GACAGTCTGC
1701 GCGTGTGTCC GCGGGGAGAA AGGACAGGCG CGGAGCCGCC AGCCCCGCT
1751 CTTGGGGGGG GTCGTCTGCC GGGAGATCGA GCAGGCCCTC GATGGTAGAC
1801 CCGTAATTGT TTTTCTGACG CGCGCGGCTG TACGCGGACC CACTTTCACA
1851 TTTAAGTTGT TTTTCTAATC CGCATATGAT CAATTCAAGG CCGAATAAGA
1901 AGGCTGGCTC TGCACCTTGG TGATCAAATA ATTGGATAGC TTGTCGTAAT
1951 AATGGCGGCA TACTATCAGT AGTAGGTGTT TCCCTTTCTT CTTTAGCGAC
2001 TTGATGCTCT TGATCTTCCA ATACGCAACC TAAAGTAAAA TGCCCCACAG
2051 CGCTGAGTGC ATATAATGCA TTCTCTAGTG AAAACCTTG TTGGCATAAA
2101 AAGGCTAATT GATTTTTCAG AGTTTCATAC TGTTTTTTCTG TAGGCCGTGT
2151 ACCTAAATGT ACTTTTGCTC CATCGCGATG ACTTAGTAAA GCACATCTAA
2201 AAC'TTTTAGC GTTATTACGT AAAAAATCTT GCCAGCTTTC CCCTTCTAAA
2251 GGGCAAAAGT GAGTATGGTG CCTATCTAAC ATCTCAATGG CTAAGGCGTC
2301 GAGCAAAGCC CGCTTATTTT TTACATGCCA ATACAATGTA GCTGCTCTA
2351 CACCTAGCTT CTGGGCGAGT TTACGGGTTG TTAAACCTTC GATTCCGACC
2401 TCATTAAGCA GCTCTAATGC GCTGTTAATC ACTTTACTTT TATCTAATCT
2451 AGACATGGTG GAAGCTTTTT GCAAAGCCT AGGCCTCCAA AAAAGCCTCC
2501 TCACTACTTC TGGAATAGCT CAGAGGCCGA GGCGGCCTCG GCCTCTGCAT
2551 AAATAAAAAA AATTAGTCAG CCATGGGGCG GAGAATGGGC GGAAGTGGC
2601 GGAGTTAGGG GCGGGATGGG CGGAGTTAGG GGCGGACTA TGGTTGCTGA
2651 CTAATTGAGA TGCATGCTTT GCATACTTCT GCCTGCTGGG GAGCCTGGGG
2701 ACTTTCCACA CCTGGTTGCT GACTAATTGA GATGCATGCT TTGCATACTT
2751 CTGCCTGCTG GGGAGCCTGG GGACTTTCCA CACCCTAACT GACACACATT
2801 CCACAGGTGC ACTAGATCGA ATTCTCAATT GTTTTACGGG GCCCAGTGCA
2851 TGGGGTCTGT CGCTCCTTTC GGTGCGGCGC TGCGGGTCGT GGGCGGGCG
2901 TCAGGCACCG GGCTTGCGGG TCATGCACCA GGTGCGCGCG TCCTTCGGGC
2951 ACTCGACGTC GCGGGTGACG GTGAAGCCGA GCCGCTCGTA GAAGGGGAGG
3001 TTGCGGGGCG GCGAGGTCTC CAGGAAGGCG GGCACCCCGG CGCGCTCGGC
3051 CGCCTCCACT CCGGGGAGCA CGACGGCGCT GCCCAGACCC TTGCCCTGGT
3101 GGTGCGGGCA GACGCGGACG GTGGCCAGGA ACCACGCGGG CTCCTTGGGC
3151 CCGTGCGGCG CCAGGAGGCC TTCCATCTGT TGCTGCGCGG CCAGCCGGGA
```

Fig. 8

- 23/35 -

```

3201 ACCGCTCAAC TCGGCCATGC GCGGGCCGAT CTCGGCGAAC ACCGCCCCCG
3251 CTTGACGCT CTCCGGCGTG GTCCAGACCG CCACCGCGGC GCCGTCGTCC
3301 GCGACCCACA CCTTGCCGAT GTGAGCCCG ACGCCGCTGA GGAAGAGTTC
3351 TTGACGCTCG GTGACCCGCT CGATGTGGCG GTCCGGATCG ACGGTGTGGC
3401 GCGTGGCGGG GTAGTCGGCG AACCGGCGG CGAGGGTGCG TACGGCCCTG
3451 GGGACGTCGT CGCGGGTGGC GAGGCGCACC GTGGGCTTGT ACTCGGTCTAT
3501 GGTAAGCTGA TCCGGCCGCG GCCTAGAGAA GGAGTGAGGG CTGGATAAAG
3551 GGAGGATTGA GCGGGGGTGC AAAGAGGAGG TTCAAGGGGG AGAGACGGCG
3601 CGGATGGAAG AAGAGGAGGC GGAGGCTTAG GGTGTACAAA GGGCTTGACC
3651 CAGGGAGGGG GGTCAAAAGC CAAGGCTTCC CAGGTCACGA TGTAGGGGAC
3701 CTGGTCTGGG TGTCCATGCG GGCCAGGTGA AAAGACCTTG ATCTTAACCT
3751 GGGTGATGAC GTCTCGGTTA AAGGTGCCGT CTCGCGGCCA TCCGACGTTA
3801 AAGGTTGGCC ATTCTGCAGA GCAGAAGGTA ACCCAACGTC TCTTCTTGAC
3851 ATCTACCGAC TGGTTGTGAG CGAGCCGCTC GACATCTTTC CAGTGATCTA
3901 AGGTCAAAC TAAGGGAGTG GTAACAGTCT GGCCCTAATT TTCAGACAAA
3951 TACAGAAACA CAGTCAGACA GAGACAACAC GAACGATGC TGCAGCAGAC
4001 AAGACGCGCG GCTTCGGTTC CAAACCGAAA GCAAAAATTC AGACGGAGGC
4051 GGGAACGTGT TTAGGTTCTC GTCTCCTACC AGAACACAT ATCCTGACGG
4101 GGTCCGATTC CACATCGACT CCCTTCTTCA GGTCCGGCCA CAAAAACGGC
4151 CCCCAAAGTC CCTGGGACGT CTCCAGGGT TCGCGCCGGG TGTCAGAAC
4201 TCGTCAGTTC CACCACGGGT CCGCCAGATA CAGAGCTAGT TAGCTAACTA
4251 GTACCGACGC AGGCGCATAA AATCAGTCAT AGACACTAGA CAATCGGACA
4301 GACACAGATA AGTTGCTGGC CAGCTTACCT CCCGGTGGTG GGTGGTGGT
4351 CCCTGGGCAG GSGTCTCCCG ATCCCGGACG AGCCCCCAA TGAAGACCC
4401 CCGCTGACGG GTAGTCAATC ACTCAGAGGA GACCTCCCA AGGAACAGCG
4451 AGACCACAAG TCGGATGCAA CTGCAAGAGG GTTATTGGA TACACGGTA
4501 CCCGGGCGAC TCAGTCAATC GGAGGACTGG CGCCCCGAGT GAGGGGTGT
4551 GGGCTCTTT ATTGAGCTCG GGGAGCAGAA GCGCCGAAC AGAAGCGAGA
4601 AGCGAACTGA TTGGTTAGTT CAAATAAGGC ACAGGGTCAT TTCAGGTCTT
4651 TGGGGCACC TGGAACATC TGATGGTTCT CTAGAACTG CTGAGGGCTG
4701 GACCGCATCT GGGGACCATC TGTCTTGGC CCTGAGCCGG CAGAGGAATC
4751 GCTTACCACA GATATCCTGT TTGGCCCATC TTCAGCTGTT CCATCTGTT
4801 TTGGCCCTGA GCCGGGCGAG GAACTGCTTA CCACAGATAT CCTGTTTGGC
4851 CCATATTCAG GCTGCAGGTG GCACTTTTCG GGGAAATGTG CGCGGAACCC
4901 CTATTGTTT ATTTTCTAA ATACATTCAA ATATGTATCC GCTCATGAGA
4951 CAATTAACCT GATAATGCT TCAATAATAT TGAAAAAGGA AGAGTATGAG
5001 TATTCAACAT TTCCGTGTCG CCCTTATTCC CTTTTTGGC GCATTTTGCC
5051 TTCCTGTTTT TGCTCACCCA GAAACGCTGG TGAAAGTAAA AGATGCTGAA
5101 GATCAGTTGG GTGCACGAGT GGGTTACATC GAACTGGATC TCAACAGCGG
5151 TAAGATCCTT GAGAGTTTTC GCGCCGAAGA ACGTTTTCCT ATGATGAGCA
5201 CTTTTAAAGT TCTGCTATGT GCGCGGTAT TATCCGTGT TGACGCGGGG
5251 CAAGAGCAAC TCGGTCCCG CATACTAT TCTCAGATG ACTTGGTTGA
5301 GTACTACCA GTACAGAAA AGCATCTTAC GGATGGCATG ACAGTAAGAG
5351 AATTATGCAG TGCTGCCATA ACCATGAGTG ATAACACTGC GGCCAACCTA
5401 CTTCTGACAA CGATCGGAG ACCGAAGGAG CTAACCGCTT TTTTGCACAA
5451 CATGGGGGAT CATGTAATC GCCTTGATCG TTGGGAACCG GAGCTGAATG
5501 AAGCCATACC AAACGACGAG CGTGACACCA CGATGCCTGT AGCAATGGCA
5551 ACAACGTTGC GCAACTATT AACTGGCGAA CTACTTACTC TAGCTTCCCG
5601 GCAACAATTA ATAGACTGGA TGGAGGCGGA TAAAGTTGCA GGACCACTTC
5651 TCGCTCGGC CCTTCCGGCT GGCTGGTTTA TTGCTGATAA ATCTGGAGCC
5701 GGTGAGCGTG GGTCTCGCGG TATCATTGCA GCACTGGGGC CAGATGGTAA
5751 GCCCTCCCGT ATCGTAGTTA TCTACACGAC GGGGAGTCAG GCAACTATGG
5801 ATGAACGAAA TAGACAGATC GCTGAGATAG GTGCCTCACT GATTAAGCAT
5851 TGGTAACGTG CAGACCAAGT TTACTCATAT ATACTTTAGA TTGATTTGCG
5901 GCCGGCCGCA AACTTCATTT TTAATTTAAA AGGATCTAGG TGAAGATCCT
5951 TTTTGATAAT CTCATGACCA AAATCCCTTA ACGTGAGTTT TCGTTCCACT
6001 GAGCGTCAGA CCCCGTAGAA AAGATCAAAG GATCTTCTTG AGATCCTTTT
6051 TTTCTGCGCG TAATCTGCTG CTTGCAACA AAAAAACCAC CGCTACCAGC
6101 GGTGGTTTGT TTGCCGGATC AAGAGCTACC AACTCTTTT CCGAAGGTAA
6151 CTGGCTTCAG CAGAGCGCAG ATACCAATA CTGTCTTCT AGTGTAGCCG
6201 TAGTTAGGCC ACCACTTCAA GAACCTGTGA GCACCGCTA CATACCTCGC
6251 TCTGCTAATC CTGTTACCAG TGGCTGCTGC CAGTGGCGAT AAGTCGTGTC
6301 TTACCGGGTT GGAATCAAGA CGATAGTTAC CGGATAAGGC GCAGCGGTCTG
6351 GGCTGAACGG GGGGTTCTGT CACACAGCCC AGCTTGGAGC GAACGACCTA
6401 CACCGAACTG AGATACCTAC AGCGTGAGCT ATGAGAAAGC GCCACGCTTC
6451 CCGAAGGAG AAAGGCGGAG AGGTATCCGG TAAGCGGCG GGTCCGAACA
6501 GGAGAGCGCA CGAGGGAGCT TCCAGGGGGA AACGCCTGGT ATCTTTATAG

```

Fig. 8

Printed: 19-10-2001

SPEC

99116533

- 24/35 -

```

6551 TCCTGTCGGG TTTCGCCACC TCTGACTTGA GCGTCGATTI TTGTCATGCT
6601 CGTCAGGGGG GCGGAGCCTA TGGAAAAACG CCAGCAACGC GGCCTTTTAA
6651 CCGTTCTCTGG COTTTTGCTG GCCTTTTGCT CACATGTTCT TTCCTGCGTT
6701 ATCCCTTGAT TCTGTGGATA ACCGTATTAC CGCCTTTGAG TGAGCTGATA
6751 CCGCTCGCCG CAGCCGAACG ACCGAGCGCA GCGAGTCAGT GAGCGAGGAA
6801 GCGGAAGAGC GCCAATACGC AAACCGCCTC TCCCGCGCGG TTGGCCGATT
6851 CATTAAATGCA ACTATGGCCA TTTAATGTAA ATACTTAAGA AAAAAACCA
6901 AATTAATTTT GATACATGCT GCATGTGAAG ACCCCCGCTG ACGGGTAGTC
6951 AATCACTCAG AGGAGACCCT CCCAAGGCAG CGAGACCACA AGTCGGAAAT
7001 GAAAGACCCC CGCTGACGGG TAGTCAATCA CTCAGAGGAG ACCCTCCCAA
7051 GGAACAGCGA GACCACAAGT CGGATGCAAC TGCAAGAGGG TTTATTGGAT
7101 ACACGGGTAC CCGGGCGACT CAGTCAATCG GAGGACTGGC GCGCCGAGTG
7151 AGGGGTTGTG GGCTCTTTTA TTGAGCTCGG GGAGCAGAAG CGCGCGAACA
7201 GAAGCGAGAA GCGAAGTATG TGGTTAGTTC AAATAAGGCA CAGGGTCATT
7251 TCAGGTCCCT GGGGCACCCCT GGAAACATCT GATGGTTCTC TAGAACTGC
7301 TGAGGGCTGG ACCGCATCTG GGGACCATCT GTTCTTGGCC CTGAGCCGGG
7351 GCAGGAACTG CTTACCACAG ATATCCTGTT TGGCCCATAT TCAGCTGTTT
7401 CATCTGTTCT TGGCCCTGAG CCGGGGCAGG AACTGCTTAC CACAGATATC
7451 CTGTTTGGCC CATATTCAGC TGTTCCATCT GTTCTTGACC TTGATCTGAA
7501 CTTCTCTATT CTCAGTTATG TATTTTCCA TGCCTTGCAA AATGGCGTTA
7551 CTTAAGCTAG CAGATCTGCT AGCTTGCCAA ACCTACAGGT GGGGTCTTTC
7601 ATTCCCCCTT TTTTCTGGAG ACTAAATAAA ATCTTTTATT TTATGCGCAC
7651 ATTTCCCCGA AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA
7701 CATTAACCTA TAAAAATAGG CGTATCACGA GGCCCTTTTC TCCGCACATT
7751 TCCCCGAAAA GTGCCACCTG ACGTCTAAGA AACCATTATT ATCATGACAT
7801 TAACCTATAA AAATAGGCGT ATCAGGAGGC CCTTTCGTCC

```

Fig. 8

- 25/35 -

pRetroOFF-U19t.sa58 Length: 8852

```

1   TCGAGTTTAC CACTCCCTAT CAGTGATAGA GAAAAGTGAA AGTCGAGTTT
51  ACCACTCCCT ATCAGTGATA GAGAAAAGTG AAAGTCGAGT TTACCACTCC
101 CTATCAGTGA TAGAGAAAGT GAAAGTCGAG TTTACCACTC CCTATCAGTG
151 ATAGAGAAAA GTGAAAGTCG AGTTTACCAC TCCCTATCAG TGATAGAGAA
201 AAGTGAAAGT CGAGTTTACC ACTCCCTATC AGTGATAGAG AAAAGTGAAG
251 TCGAGTTTAC CACTCCCTAT CAGTGATAGA GAAAAGTGAA AGTCGAGCTC
301 GGTACCCGGG TCGAGTAGGC GTGTACGGTG GGAGGCCTAT ATAAGCAGAG
351 CTCGTTTAGT GAACCGTCAG ATCGCCTGGA GACGCCATCC ACGCTGTTTT
401 GACCTCCATA GAAGACACCG GGACCGATCC AGCCTGCGGC CGCTTAATTA
451 AGTTTAAACG GATCCxxxxx xxxxxxatgc catctagtga tgatgaggct
501 actgctgact ctcaacattc tactcctcca aaaaagaaga gaaggttaga
551 agacccaag gactttcctt cagaattgct aagttttttg agtcatgctg
601 tgttttagtaa tagaactcct gcttgcttg ctatttacac cacaagga
651 aaagctgcac tgcatacaaa gaaaattatg gaaaaatatt ctgtaacctt
701 tataagtagg cataacagtt ataatacata catactgttt tttcttactc
751 cacacaggca tagagtgtct gctattaata actatgctca aaaatttgtt
801 acctttagct ttttaatttg taaaggggtt aataaggaat atttgatgta
851 tagtgcttg actagagatc cattttctgt tattgaggaa agtttgccag
901 gtgggttaaa ggagcatgat tttaatccag aagaagcaga ggaactaaa
951 caagtgtcct ggaagcttgt aacagagtat gcaatggaaa caaatgtga
1001 tcatgtgttg tlatgtcttg ggatgtactt ggaatttcag tacagttttg
1051 aaatgtgttt aaaatgtatt aaaaaagaac agcccagcca ctataagtac
1101 catgaaaagc attatgcaaa tgctgtcata tttgttgaca gcaaaaacca
1151 aaaaaccata tqccaacagg ctgttgatac tgttttagct aaaaagcggg
1201 tcatagacct acaattaaat agagaacaaa tgttaacaaa cagatttaat
1251 gatcttttgg ataggatgga tataatgttt ggttctacag gctctgtga
1301 catagaagaa tggatggctg gagttgcttg gctacactgt ttgttgccca
1351 aaatggattc agtggtgtat gactttttaa aatgcatggt gtacaacatt
1401 cctaaaaaaa gatactggct gtttaaagga ccaattgata gtggtaaaac
1451 tacattagca gctgctttgc ttgaattatg tggggggaag gctttaaatg
1501 ttaatttggc cttggacagg ctgaactttg agctaggagt agctattgac
1551 cagtttttag tagtttttga ggatgtaaag ggcactggag gggagtccag
1601 agatttgcct tcaggtcagg gaattaataa cctggacaat ttaagggatt
1651 atttggatgg cagtgttaag gtaaaactag aaaagaaaca cctaaataaa
1701 agaactcaaa tatttccccc tggaaatagt accatgaatg agtacagtgt
1751 gcctaaaaaa ctgcaggcca gatttgtaaa acaaatagat tttaggccca
1801 aagattatct aaagcattgc ctggaacgca gtgagttttt gttagaaaag
1851 agaataatc aaagtggcat tgctttgctt cttatgttaa tttggtacag
1901 acctgtggct gagtttgcct aaagtattca ggcagaattt gtggagtggg
1951 aagagagatt ggacaaagag tttagtttgt cagtgtatca aaaaatgaag
2001 ttaatgtgg ctatgggaat tggagtttta gattggctaa gaaacagtga
2051 tgatgatgat gaagacagcc aggaaaatgc tgataaaaat gaagatggtg
2101 gggagaagaa catggaagac tcagggcatg aaacagcatg tgattcacag
2151 tcccaaggct catttcaggc ccctcagtc cccacagtct ttcattgaca
2201 laatacagcca taccacattt gtagagggtt tacttgcttt aaaaaacctc
2251 ccacacctcc ccctgaacct gaaacataax xxxxxxxxxx ggatcccccg
2301 GGAACAACAA CAATTGCATT CATTTTATGT TTCAGGTTCA GGGGGAGGTG
2351 TGGGAGGTTT TTAAAGCAA GTAAAACCTC TACAAATGTG GTATGGCTGA
2401 TTATGATCCT GCAAGCCTCG TCGTCTGGCC GGACCACGCT ATCTGTGCAA
2451 GGTCCCGGGA CGCGCGCTCC ATGAGCAGAG CGTCGCGCCC CCTACCCACC
2501 GTACTCGTCA ATTCCAAGGG CATCGGTAAA CAGAGCGCCG TAGGGGGCGG
2551 AGTCGTGGGG GGTAAATCCC GGACCCGGGG AATCCCGGTC CCCCAACATG
2601 TCCAGATCGA AATCGTCTAG CGCGTCGGCA TGCGCCATCG CCACGTCCTC
2651 GCCGTATAAG TGGAGCTCGT CCCCAGGCT GACATCGGTC GGGGGGGCGG
2701 TCGACAGTCT GCGCGTGTGT CCGCGGGGAG AAAGGACAGG CGCGGAGCCG
2751 CCAGCCCCGC CTCTTCGGGG GCGTCGTCGT CCGGGAGATC GAGCAGGCCC
2801 TCGATGGTAG ACCCGTAATT GTTTTTCGTA CGCGCGCGGC TGTACGCGGA
2851 CCCACTTTCA CATTTAAGTT GTTTTCTAA TCCGCATATG ATCAATTCAA
2901 GCCCGAATAA GAAGGCTGGC TCTGCACCTT GGTGATCAAA TAATTCGATA
2951 GCTTGTCTGA ATAATGGCG CATACTATCA GTAGTAGGTG TTTCCCTTTC
3001 TTCTTTAGCG ACTTGATGCT CTTGATCTTC CAATACGCAA CCTAAAGTAA
3051 AATGCCCCAC AGCGCTGAGT GCATATAATG CATTTCTTAG TGAAAAACCT
3101 TGTTGGCATA AAAAGGCTAA TTGATTTTCG AGAGTTTCAT ACTGTTTTTC
3151 TGTAGGCCGT GTACCTAAAT GTACTTTTGC TCCATCGCGA TGACTTAGTA
3201 AAGCACATCT AAAACTTTTA GCGTTATTAC GTAAAAATC TTGCCAGCTT

```

Fig. 9

- 26/35 -

```

3251 TCCCTTCTA AAGGGCAAAA GTGAGTATGG TGCCTATCTA ACATCTCAAT
3301 GGCTAAGGCG TCGAGCAAAAG CCCGCTTATT TTTTACATCC CAATACAATG
3351 TAGGCTGCTC TACACCTAGC TTCTGGGCGA GTTTACGGGT TGTAAACCT
3401 TCGATTCCGA CCTCATTAAG CAGCTCTAAT GCGCTGTAA TCACTTTACT
3451 TTTATCTAAT CTAGACATGG TGGAAGCTTT TTGCAAAAGC CTAGGCCCTCC
3501 AAAAAAGCCT CCTCACTACT TCTGGAATAG CTCAGAGGCC GAGGCGGCCCT
3551 CGGCTCTGCT ATAAATAAAA AAAATTAGTC AGCCATGGGG CGGAGAATGG
3601 GCGGAAGTGG GCGGAGTTAG GCGCGGATG GCGGAGTTA GGGCGGGAC
3651 TATGTTGCT GACTAATTGA GATGCATGCT TTGCATACTT CTGCTCTCTG
3701 GGGAGCCTGG GGAATTCCA CACCTGTTG CTGACTAATT CAGATGCATG
3751 CTTTGCATAC TTCTGCCTGC TGGGAGCCT GGGGACTTTC CACACCTAA
3801 CTGACACACA TTCCACAGGT CGACTAGATC GAATTCTCAA TTGTTTTACG
3851 CGGCCCCGATG CATGGGGTGG TCGCTCTCTT TCGGTCGGGC GCTGCGGGT
3901 GTGGGGCGGG CGTCAGGCAC GGGGCTGCG GGTATGCAC CAGGTGCGC
3951 GTCTCTTGG GCACTCGACG TCGGCGGTGA CCGTGAAGCC GAGCGGCTCG
4001 TAGAAGGGGA GGTTCGGGG CGCGAGGTC TCCAGGAAG CGGGCACCCC
4051 GCGCGCTCG GCGGCTCCA CTCGCGGAG CACGACGGC CTGCCAGAC
4101 CCTTGCCCTG GTGTCGGGC GAGACGCCA CCGTGGCCAG GAACCACGG
4151 GGCTCCTTGG GCGGTCGGG CGCCAGGAG CTTCCATCT GTTGTGCGC
4201 GGCCAGCGG GAACCGCTCA ACTCGGCCAT GCGCGGGCCG ATCTCGGCGA
4251 ACACCGCCCC CGCTTCGACG CTCTCCGGC TGGTCCAGC CGCCACCGC
4301 GCGCUGTCTG CCGCGACCCA CACCTTGCCG ATGTCGAGC CGACGCGCT
4351 GAGGAAGAGT TCTTGCAGCT CCGTGACCCG CTCGATGTGG CCGTCCGGAT
4401 CGACGGTGTG GCGGTGGCG GGTAGTGGG CGAACGCGC GCGAGGGTG
4451 CGTACGGCCC TGGGACGTC TCGCGGGTG GCGAGCGCA CCGTGGGCTT
4501 GTACTCGGTC ATGGTAAGCT GATCCGGCCG GCGCTAGAG AAGGAGTGAG
4551 GGCTGGATAA AGGGAGGATT GAGGCGGGGT CGAAGAGGA GGTTCAGGG
4601 GGAGAGACGG CGCGGATGA AGAAGAGGAG GCGGAGGCTT AGGGTGTACA
4651 AAGGGCTTGA CCCAGGGAG GGGGTCAAAA GCCAAGGCTT CCGAGGTCAC
4701 GATGTAGGGG ACCTGGTCTG GGTGTCCATG CCGGCCAGGT GAAAAGACCT
4751 TGATCTTAAC CTGGGTGATG AGGTCTCGGT TAAAGTGCC GTCTCGCGC
4801 CATCCGACGT TAAAGGTTGG CCATTCTGCA GAGCAGAAG TAACCCAACG
4851 TCTCTTCTTG ACATCTACCG ACTGGTTGTG AGCGAGCCG TCGACATCTT
4901 TCCAGTGATC TAAGGTCAA CTTAAGGGAG TGGTAACAGT CTGGCCCTAA
4951 TTTTCAGACA AATACAGAAA CACAGTCAGA CAGAGACAAC ACAGAAGAT
5001 GCTGCAGCAG ACAAGACGG CGGCTTCGGT TCCAAACCGA AAGCAAAAT
5051 TCAGACGGAG GCGGGAAGT TTTTAGGTTT TCGTCTCCTA CCAGAACCAC
5101 ATATCCTGAC GGGGTGGAT TCCACATCGA CTCCCTTCCT CAGGTGGGG
5151 CACAAAACG GCGCCAAAG TCCCTGGGAC GTCTCCAGG GTTGGGGCG
5201 GGTGTTTCA ACTGTCAGT TCCACCAGG GTCCGCCAGA TACAGGCTA
5251 GTTAGCTAAC TAGTACCGAC GCAGGCGCAT AAAATCAGT ATAGACACTA
5301 GACAATCGGA CAGACACAGA TAAGTTGCTG GCCAGCTTAC CTCCCGGTGG
5351 TGGGTGGGTG GTCCCTGGGC AGGGGTCTCC CGATCCCGGA CGAGCCCCCA
5401 AATGAAAGAC CCGGCTGAC GGGTAGTCAA TCACTCAGAG GAGACCTCC
5451 CAAGAACAG CGAGACCACA AGTCGGATGC AACTGCAAGA GGGTTTATTG
5501 GATACACGGG TACCGGGCG ACTCAGTCAA TCGGAGGACT GCGCCCCGA
5551 GTGAGGGGTT GTGGGCTCTT TTATTGAGCT CGGGGAGCAG AAGCGCGCGA
5601 ACAGAAGCGA GAAGCGAAGT GATTGGTTAG TTCAAATAAG GCACAGGGTC
5651 ATTTCAGGTC CTTGGGGCAC CCTGGAAACA TCTGATGGTT CTCTAGAAAC
5701 TGCTGAGGGC TGGACCGCAT CTGGGGACCA TCTGTTCTTG GCCCTGAGCC
5751 GGGGCAGGAA CTGCTTACCA CAGATATCCT GTTTGGCCCA TATTGAGCTG
5801 TTCCATCTGT TCTTGGCCCT GAGCCGGGGC AGGAAGTGCT TACCACAGAT
5851 ATCCTGTTTG GCGCATATTC AGGCTGCAGG TGGCACTTTT CGGGGAAATG
5901 TGCGCGGAAC CCCTATTTGT TTATTTTCT AAATACATTC AAATATGTAT
5951 CCGCTCATGA GACAATAACC CTGATAAATG CTTCAATAAT ATTGAAAAAG
6001 GAAGAGTATG AGTATTCAC ATTTCGCTG CGCCCTTATT CCTTTTTTG
6051 CGGCATTTTG CCTTCTGTT TTTGCTCACC CAGAAACGCT GGTGAAAGTA
6101 AAAGATGCTG AAGATCAGTT GGGTGCACGA GTGGGTTACA TCGAACTGGA
6151 TCTCAACACC GGTAAGATCC TTGAGAGTTT TCGCCCGAA GAACGTTTTT
6201 CAATGATGAG CACTTTTAA GTTCTGCTAT GTGGCGGGT ATTATCCCGT
6251 GTTGACGCGG GCGAAGAGCA ACTCGGTCG CGCATACACT ATTCTCAGAA
6301 TGACTTGGTT GAGTACTCAC CAGTCACAGA AAAGCATCTT ACGGATGGCA
6351 TGACAGTAAG AGAATTATG AGTGCTGCCA TAACCATGAG TGATAACACT
6401 GCGGCCAACT TACTCTGAC AACGATCGGA GGACCGAAGG AGCTAACCGC
6451 TTTTTTGCAC AACATGGGG ATCATGTAAC TCGCTTGAT CCGTGGGAAC
6501 CGAGCTGAA TGAAGCCATA CCAACGACG AGCGTGACAC CAGGATGCCCT
6551 GTAGCAATGG CAACAACGTT GCGCAACTA TTAAGTGCG AACTACTTAC

```

Fig. 9

- 27/35 -

```

6601 TCTAGCTTCC CGGCAACAAT TAATAGACTG GATGGAGGCG GATAAAGTTG
6651 CAGGACCACT TCTGCGCTCG GCCCTTCCGG CTGGCTGGTT TATTGCTGAT
6701 AAATCTGGAG CCGGTGAGCG TGGGTCTCGC GGTATCATTG CAGCACTGGG
6751 GCCAGATGGT AAGCCCTCCC GTATCGTAGT TATCTACACG ACGGGGAGTC
6801 AGGCAACTAT GGATGAACGA AATAGACAGA TCGCTGAGAT AGGTGCCTCA
6851 CTGATTAAGC ATTGGTAACT GTCAGACCAA GTTTACTCAT ATATACTTTA
6901 GATTGATTTG CGGCCGGCCG CAACTTTCAT TTTTAATTTA AAAGGATCTA
6951 GGTGAAGATC CTTTTTGATA ATCTCATGAC CAAAATCCCT TAACGTGAGT
7001 TTTCGTTCCA CTGAGCGTCA GACCCCGTAG AAAAGATCAA AGGATCTTCT
7051 TGAGATCCTT TTTTCTGCG CGTAATCTGC TGCTTGCAAA CAAAAAACC
7101 ACCGCTACCA GCGGTGGTTT GTTTGCCGGA TCAAGAGCTA CCAACTCTTT
7151 TTCCGAAGGT AACTGGCTTC AGCAGAGCGC AGATACCAA TACTGTCTTT
7201 CTAGTGTAGC CGTAGTTAGG CCACCACTTC AAGAACTCTG TAGCACCGCC
7251 TACATACCTC GCTCTGCTAA TCCTGTTACC AGTGGCTGCT GCCAGTGGCG
7301 ATAAGTCTGT TCTTACCGGG TGGACTCAA GACGATAGTT ACCGGATAAG
7351 GCGCAGCGGT CGGCTGAAC GGGGGGTTCC TGACACACAGC CCAGCTTGGA
7401 GCGAACGACC TACACCGAAC TGAGATACCT ACAGCGTGAG CTATGAGAAA
7451 GCGCCACGCT TCCCGAAGGG AGAAGGCGG ACAGGTATCC GGTAAGCGGC
7501 AGGTCGGAA CAGGAGAGCG CACGAGGAG CTTCAGGGG GAAACGCCGT
7551 GTATCTTTAT AGTCCTGTCT GGTTCGCCA CCTCTGACTT GAGCGTCGAT
7601 TTTTGTGATG CTCGTCAGGG GGGCGGAGCC TATGGAAAAA CGCCAGCAAC
7651 GCGGCTTTT TACGGTTCCT GGCTTTTTCG TGCCCTTTTG CTCACATGTT
7701 CTTTCCTGCG TTATCCCTTG ATTCTGTGGA TAACCGTATT ACCGCTTTTG
7751 AGTGAGCTGA TACCGCTCGC CGCAGCCGAA CGACCGAGCG CAGCGAGTCA
7801 GTGAGCGAGG AAGCGGAAGA GCGCCAATAC GCAAACCGCC TCTCCCGCG
7851 CGTTGGCCGA TTCATTAATG CAACTATGGC CATTTAATGT AAATACTTAA
7901 GAAAAAAAC CAAATTAATT TTGATACATG CTGCATGTGA AGACCCCCGC
7951 TGACGGGTAG TCAATCACTC AGAGGAGACC CTCCAAGGC AGCGAGACCA
8001 CAAGTCGGAA ATGAAAGACC CCCGCTGACG GGTAGTCAAT CACTCAGAGG
8051 AGACCCCTCC AAGGAACAGC GAGACCACAA GTCGGATGCA ACTGCAAGAG
8101 GGTTFATTGG ATACACGGGT ACCCGGGCGA CTCAGTCAAT CGGAGGACTG
8151 GCGCCCCGAG TGAGGGGTTG TGGGCTCTTT TATTGAGCTC GGGGAGCAGA
8201 AGCGCGCGAA CAGAAGCGAG AAGCGAACTG ATTGGTTAGT TCAAATAAGG
8251 CACAGGGTCA TTTCAGGTCC TTGGGGCACC CTGGAAACAT CTGATGGTTC
8301 TCTAGAAACT GCTGAGGGCT GGACCGCATC TGGGGACCAT CTGTTCTTGG
8351 CCTGAGCCG GGGCAGGAAC TGCTTACCAC AGATATCCTG TTTGGCCCAT
8401 ATTCAGCTGT TCCATCTGTT CTTGGCCCTG AGCCGGGGCA GGAAGTCTT
8451 ACCACAGATA TCCTGTTTGG CCCATATTCA GCTGTTCCAT CTGTTCTTGA
8501 CCTTGATCTG AACTTCTCTA TTCTCAGTTA TGTATTTTTC CATGCCTTGC
8551 AAAATGGCGT TACTTAAGCT AGCAGATCTG CTAGCTTGCC AAACCTACAG
8601 GTGGGGTCTT TCATTCCCC CTTTTCTGG AGACTAAATA AAATCTTTTA
8651 TTTTATGCGC ACATTTCCCC GAAAAGTGCC ACCTGACGTC TAAGAAACCA
8701 TTATTATCAT GACATTAACC TATAAAATA GGCGTATCAC GAGGCCCTTT
8751 CGTCCGCACA TTTCCCGGAA AAGTGCCACC TGACGTCTAA GAAACCATTA
8801 TTATCATGAC ATTAACCTAT AAAAATAGGC GTATCACGAG GCCCTTTCGT
8851 CC

```

Fig. 9

Printed: 19-10-2001

SPEC

99116533

- 28/35 -

puhd10-3-h173 Length: 3621

```

1   ctcgagttta ccactcccta tcagtqatag agaaaagtga aagtcgagtt
51  taaccactccc tatcagtgat agagaaaagt gaaagtcgag tttaccactc
101 cctatcagtg atagaga aa gtgaaagtcg agtttaccac tccctatcag
151 tgatagagaaa aagtgaagt cgagtttacc actccotatc agtgatagag
201 aaaagtgaata gtcgagttta ccactcccta tcagtqatag agaaaagtga
251 aagtcgagtt taccactccc tatcagtgat agagaaaagt gaaagtcgag
301 ctcggtacccc ggcgtcgagta ggcgtgtacg gtgggaggcc tatataagca
351 gagctcgttt agtgaaccgt cagatcgcc tggagacgca tccacgctgt
401 tttgacctcc atagaagaca ccgggaccga tccagcctcc gcggccccga
451 attaaacagt cgagctacgt caacgaaaaa taaaatccaa acatgagccg
501 cctgcccgtc ctgctcctgc tccaactcct ggtccgcccc ggactccaag
551 ctcccatgac ccagacaacg tccctgaaga caagctgggt taactgctct
601 aacatgatcg atgaaattat aacacactta aagcagccac ctttgccctt
651 gctggacttc aacaacctca atggggaaga ccaagacatt ctgatggaaa
701 ataaccttcg aaggccaaac ctggaggcat tcaacagggc tgtcaagagt
751 ttacagaacg catcagcaat tgagagcatt cttaaaaatc tctgccatg
801 tctgcccctg gccacggccg caccacgcg acatccaatc catatcaagg
851 acggtgactg gaatgaattc cggaggaaac tgacgttcta tctgaaaaac
901 cttgagaatg cgcaggctca acagacgact ttgagcctcg cgatctttta
951 gaactcgact ctgacatga taagatacat tgatgagttt ggacaaacca
1001 caactgaat gcagtgaata aaatgcttta tttgtgaaat ttgtgatgct
1051 attgctttat ttgtaacctat tataagctgc aataaacaag ttaacaacaa
1101 caattgcatt cattttatgt ttcaggttca gggggagggtg tggggagggtt
1151 cttaaagcaa gtaaaacctc tacaatgtg gtatggctga ttatgatcct
1201 gcaagcctcg tcgtctggcc ggaaccaagc atctgtgcaa ggtccccgga
1251 cgcgcgctcc atgagcagag cgcgcgcgc cgaggcaaga ctcgggcggc
1301 gccctgcccg tcccaccagg tcaacaggcg gtaaccggcc tcttcatcgg
1351 gaatgcgcgc gaccttcagc atcgccggca tgtccctgg cggacgggaa
1401 gtatcagctc gaccaagctt ggcgagattt tcaggagcta aggaagctaa
1451 aatggagaaa aaaatcactg gatataccac cgttgatata tcccaatggc
1501 atcgtaaaga acattttgag gcatttcagt cagttgctca atgtacctat
1551 aaccagaccg ttcaactgca ttaatgaatc ggccaacgcg cggggagagg
1601 cggtttgogt attggggcgt ctcccgcttc ctgcctcact gactcgctgc
1651 gctcggtcgt tcggctggcg cagcggttat cagctcactc aaagtccgta
1701 atacggttat ccacagaatc aggggataac gcaggaaaaga acatgtgagc
1751 aaaaggccag caaaaaggcca ggaaccgtaa aagggcgcg ttgctggcgt
1801 tttrccatag gctccgcccc cctgacgagc atcacaaaaa tgcacgctca
1851 agtcagaggt ggcgaaaccc gacaggacta taaagatacc aggcgtttcc
1901 ccctggaagc tccctcgtgc gctctcctgt tccgacctg ccgcttaccg
1951 gatacctgtc cgcctttctc ccttcgggaa gsgtgcgct tctcaatgc
2001 tcacgctgta ggtatctcag ttcggtgtag gtcgttcgct ccaagctggg
2051 ctgtgtgcac gaaccccccg ttcaagccga ccgctgcgcc ttatccggtg
2101 actatcgtct tgagtcacac ccggttaagac acgacttatc gccactggaa
2151 gcagccactg gtaacaggat tagcagagcg aggtatgtag gcggtgctac
2201 aaggttcttg aagtgggtgc ctaactacgg ctacactaga aggcagtat
2251 ttggtatctg cgtctgctg aagccagtta ccttcggaaa aagagttggt
2301 agctcttgat ccggcaaaac aaccaccgct ggtagcggtg gttttttgt
2351 ttgcaagcag cagattacgc gcagaaaaaa aggatctcaa gaagatcctt
2401 tgatcttttc tacggggtct gacgctcagt ggaacgaaaa ctacggttaa
2451 gggatttttg tcatgagatt atcaaaaagg atcttcacct agatcctttt
2501 aaattaaaaa tgaagtttta aatcaatcta aagtatatat gagtaaaactt
2551 ggtctgacag ttaccaatgc ttaatcagtg aggcacctat ctacgcatc
2601 tgtctatttc gtrcatccat agttgctga ctcoccytcg tgtagataac
2651 tacgatacgg gagggcttac carctggccc cagtgctgca atgataccgc
2701 gagaaccacg ctcacgggct ccagatttat cagcaataaa ccagccagcc
2751 ggaaggggcg agcgagaaag tggctctgca actttatccg cctccatcca
2801 gtctattaat tgttgccggg aagctagagt aagtagttcg ccagttaata
2851 gtttgcgcaa cgttgttgcc attgctacag gcacgtgtg gtcacgctcg
2901 tcgttttgta tggcttcatt cagctccggt tcccaacgat caaggcgagt
2951 tacatgatcc cccatgttgt gcaaaaaaag ggttagctcc ttcggtctc
3001 cgaatcgttg cagaagtaag ttggccgcag tgttatcact catggttatg
3051 gcagcactgc ataattctct tactgtcatg ccacccgtaa gatgcttttc
3101 tqtgactggt gagtactcaa ccaagtcatt ctgagaatag tgtatgcggc
3151 gaccgagttg ctcttgcggc tegtcaatac gggataatac ccgcccacat
3201 aqcagaactt taaaagtgtc catcattgga aaacggtctt cggggcgaaa

```

Fig. 10

- 29/35 -

```
3251 actctcaagg atcttaccgc tgttgagatc cagttcgatg taaccactc
3301 gtgcacccaa ctgatcttca gcatcttcta ctttcaccag cgtttctggg
3351 tgagcaaaaa caggaaggca aaatgccgca aaaaaggga taaggcgac
3401 acggaaatgt tgaatactca tactcttcct ttttcaatat tattgaagca
3451 ttatctaggg ttattgtctc atgagcggat acatatctga atgtatttag
3501 aaaaataaac aaataggggt tccgcgcaca ttcccccga aagtccacc
3551 tgangtctaa gaaaccatta ttatcatgac attaacctat aaaaataggc
3601 gtatcacgag gcccttccgt c
```

Fig. 10

pUND10-3-HIL6

Length: 3752 June 22, 1999 10:32 Type: N Check: 8139 ..

```

1  ctccaggttta ccaactcccta tcagtgatag agaaaaagtga aagtcaggtt
51  taccactccc tatcaqtgat agagaaaagt gaaagtcgag tttaccactc
101 cctatccagng atagagaaaa gtgaaagtcg agtttaccac tucctatcag
151 tgaatagagaa aagtgaaggt cgagttttacc actccctatc agtgatagag
201 aaaaagtgaaa gtccaggttta ccaactcccta tcagtgatag agaaaaagtga
251 aagtcaggtt taccactccc tatcaqtgat agagaaaagt gaaagtcgag
301 ctccgttacc qggtcgagta ggcgtgtagc gtgggaggcc tatataagca
351 gagctcggtt agtgaaccgt cagatcgccct ggagacgcca tccacgctgt
401 tttgacctcc atagaagaca ccgggaccca tccagccctcc ggcgtggcgg
451 ccgctctaga actagtggtt cccccagctt acctgccatg ccagtacccc
501 caggagaaga ttccaaagat gtagccgccc cacacagaca gccactcacc
551 tcttcagaac gaattgacaa acaaattcgg tacatcctcg accgcarctc
601 agcccttga aagagacat gtaacaagag taacatgtgt gaaagcagca
651 aagaggcact ggcagaaaaa aacctgaacc ttcnaaagat ggctgaaaaa
701 gatggatgct tccaatctgg attcaatgag gagaattgcc tggtgaaaat
751 catcactggt cttltggagt ttgaggtata cctagaglac ctccagaaca
801 gatttgagag tagtgaggaa caagccagag ctgtccagat gagtacaaaa
851 gtccctgact aqtcctgca gaaaaaggca aagaattctag atgcaataac
901 cacccttgac ccaaccacaa atgccagcct gctgagcaag ctgcaggcac
951 agaaccagtg qctgcaggac atgacaactc atctcattct gcgcagcttt
1001 aaggagttcc tgcagtccag cctgagggtt cttcggaaaa tgtagtaagg
1051 atccgaattc gagctcggtt cccggggatc ctctagagga tccagacatg
1101 ataagataca ttgatgagtt tggacaaacc acaactagaa tgcagtgaia
1151 aaaaatgctt atttgtgaaa tttgtgatgc tatgtcttta tttgtaacca
1201 ttataagctg caataaacia gttaaacaa acaattgcat tcattttatg
1251 tttcaqgttc agqgggaggt gtgggaggtt ttttaaagca agtaaaacct
1301 ctacnaatql ggtatggtg attatgatcc tgaagcctc gtcgtctggc
1351 cggaccacgc tatctgtgca aggtcccgcc acgcgcgctc catgagcaga
1401 gcgcgccgag ccgaggcaag actcggggcg ccgcctgccc gtcccaccag
1451 gtcaaccagg qgtaacccgc ctcttcacgc ggaatgcgag cgaccttcag
1501 catcgccgag atgtccctg gcggacggga agtatcagct cgaccaagct
1551 tggcgagatt ttcaggagct aaggaaagcta aaatggagaa aaaaatcact
1601 ggaratacaa ccgttgatat atcccaatgg catcgtaaa aacattttga
1651 ggcatttcag tcagttgctc aatgtacct taaccagacc gttcagctgc
1701 attaatgaat ccgcacaacc gcggggagag gcggtttgag tattggcgcg
1751 tcttcgcgtt cctcgctcac tgactcgctg cgtcggctcg ttcggctgag
1801 gcgagcggtt tcagctcact caaagtcggt aatacggtta tccacagaat
1851 caggggataa cgcagyaag aacatgtgag caaaaggcca gcaaaaggcc
1901 aggaaccgta aaaaaggccc gttgctggcg tttttccata ggctccgccc
1951 ccttgacgag catvacaana atcgacgctc aagtcagagg tggcgaaacc
2001 cgcacaggact araaagalac caggcggttc cccctggaag ctccctggtg
2051 cgtctcctg ttccgacctt gccgcttacc ggatacctgt ccgcctttct
2101 ccttcgggga agcgtggcgc tttctcaatg ctacgctgt aggtatctca
2151 gttcgggtga ggtcgttcgc tccaaagctg gctgtgtgca ccaaccccc
2201 gttcagcccg accgctggcg cttatccggt aactatcgct ttgagtccaa
2251 cccggtaaga cagcacttat cgcactgga agcagccact ggtaacagga
2301 ttagcagagc gaggtatqla ggcgggtgcta caqagttctt gaagtgggtg
2351 cctaactacg qctacactag aaggacagta tttggtatct gcgctctgct
2401 gaagccaqtl accttcggaa aaagagttgg tagctcttga tccggcaaac
2451 aaacnaccgc tggtagcggt ggtttttttg tttgcaagca gcagattacg
2501 cgcagaaaaa aaggatctca agaagatcct ttgatctttt ctacgggtc
2551 tgacggtcag tggaaacgaa actcacgtta agggattttg gtcattgagat
2601 tatcaaaaaa gactttcacc tagatccttt tauattaaaa atgaagttt
2651 aatatcaatc aaagtatata lgagttaact tgggtctgaca gttacnaatg
2701 ctlaatcaqt gaggcacctt tcttagogat ctgtctatit cgttcaccca
2751 tagtlycctq actcccgctc gtgtagataa ctacgatacg ygggggtta
2801 caatctggcc ccagtgtgtc aatgataccg cgagaccac gctcaccggc
2851 tccagattta tcagcaahaa accagccagc cgggaaggcc gagcgagaa
2901 gtggtcctgc aactttatcc gctccatcc aqtctattaa ttggtggcgg
2951 gaagctagag taagtagttc gccagttaat agtttgcgca acggtgttgc
3001 nathtgctaca ggcactggtt ggtcacgctc gtcgtttggt atggctctat
3051 ttagctcggg ttcccaacga tcaaggcgag ttacatgac ccccatgtg
3101 tgcataaaag ccgttagctc ctccggtcct ccgagctgtg tcaagaagtaa
3151 gntggccgca gtgttatcac tcatggttat ggcagcactg cataatctc

```

Fig. 11

- 31/35 -

| | | | | | |
|------|------------|------------|------------|------------|------------|
| 3201 | ctactgtcat | gccalcgta | agatgctttt | ctgtgactgg | tgagtactca |
| 3251 | accaagtcac | tctgagaata | gtgtatgcgg | cgaccgagtc | gctcttgccc |
| 3301 | gtcgtcaata | cgggataata | ccgcgccaca | tagcagaact | ttaaaagtgc |
| 3351 | tcatcattgg | aaaacgttct | tcggggcgaa | aactctcaag | gatcttaccg |
| 3401 | ctgttgagat | ccagttcgat | gtaaccact | cgtgcacca | actgatcttc |
| 3451 | agcactcttt | actttcacca | gcgtttctgg | gtgagcaaaa | acaggaaggc |
| 3501 | aaaatgccgc | aaaaaaggga | ataaggcgca | cacggaaatg | ttgaatactc |
| 3551 | atactcttcc | tttttcaata | ttattgaagc | atttatcagg | gttattgtct |
| 3601 | catgagcgga | cacatatttg | aatgtattta | gaaaaataaa | caaatagggg |
| 3651 | ttccgcgcac | atttcccga | aaagtgccac | ctgacgcta | agaaaccatt |
| 3701 | attatcatga | caltaacctc | taaaaatagg | cgtatcacga | ggccctttcg |
| 3751 | tc | | | | |

Fig. 11

- 32/35 -

puhd10-3-tgf

```

1  ctccgagtttandactccctatcagtgatagagaaaagtgaaagtcgagtttaccactccc 60
   -----+-----+-----+-----+-----+-----+-----+-----+
61  tatcagtgatagagaaaagtgaaagtcgagtttaccactccctatcagtgatagagaaaa 120
   -----+-----+-----+-----+-----+-----+-----+-----+
121 gtgaaagtcgagtttaccactccctatcagtgatagagaaaagtgaaagtcgagtttacc 160
   -----+-----+-----+-----+-----+-----+-----+-----+
181 actccctatcagtgatagagaaaagtgaaagtcgagtttaccactccctatcagtgatag 240
   -----+-----+-----+-----+-----+-----+-----+-----+
241 agaaaagtgaaagtcgagtttaccactccctatcagtgatagagaaaagtgaaagtcgag 300
   -----+-----+-----+-----+-----+-----+-----+-----+
301 ctccggtaccgggtcgagtggcggtgtacgggtgggagggcctatatataagcagagctcgttt 360
   -----+-----+-----+-----+-----+-----+-----+-----+
361 agtgaaccggtcagatcgccctggagacgccatccacgctgttttgacctccatagaagaca 420
   -----+-----+-----+-----+-----+-----+-----+-----+
421 ccgggaccgatccagcctccggggcccggaattcctgcagcccATGCACTTGCAAAGGGC 480
   -----+-----+-----+-----+-----+-----+-----+-----+
481 TCTGGTAGTCCCTGGCCCTGCTGAACTTGGCCACAATCAGCCTCTCTCTGTCCACTTGCAC 540
   -----+-----+-----+-----+-----+-----+-----+-----+
541 CACGTTGGACTTCGGCCACATCAAGAAGAAGAGGGTGAAGCCATTAGGGGACAGATCTT 600
   -----+-----+-----+-----+-----+-----+-----+-----+
601 GAGCAAGCTCAGGCTCACCAGCCCCCTGAGCCATCGGTGATGACCCACGTCCCCCTATCA 660
   -----+-----+-----+-----+-----+-----+-----+-----+
661 GGTCCTGGCACTTTACAACAGCACCCGGGAGTTGCTGGAAGAGATGCACGGGGAGAGGGA 720
   -----+-----+-----+-----+-----+-----+-----+-----+
721 GGAAGGCTGCACTCAGGAGACCTCGGAGTCTGAGTACTATGCCAAAGAGATCCATAAATT 780
   -----+-----+-----+-----+-----+-----+-----+-----+
781 CGACATGATCCAGGGACTGGCGGAGCACAAATGAACTGGCCGTCTGCCCCAAAGGAATTAC 840
   -----+-----+-----+-----+-----+-----+-----+-----+
841 CTCTAAGGTTTTTCGTTTCAATGTGTCTCAGTGGAGAAAAATGGAACCAATCTGTTCCG 900
   -----+-----+-----+-----+-----+-----+-----+-----+
901 GCCAGAGTTCGCGGTCTTGCGGGTGCCCAACCCAGCTCCAAGCGCACAGAGCAGAGAAT 960
   -----+-----+-----+-----+-----+-----+-----+-----+
961 TGAGCTCTTCCAGATACTTCGACCGGATGAGCACATAGCCAAGCAGCGCTACATAGGTGG 1020
   -----+-----+-----+-----+-----+-----+-----+-----+
1021 CAAGAATCTGCCCCACAAGGGGCACCGCTGAATGGCTGTCTTTCGATGTCACTGACACTGT 1080
   -----+-----+-----+-----+-----+-----+-----+-----+
1081 GCGCGAGTGGCTGTTGAGGAGAGAGTCCAACCTTGGGTCTGGAAATCAGCATCCACTGTCC 1140
   -----+-----+-----+-----+-----+-----+-----+-----+
1141 ATGTCACACCTTTCAGCCCAATGGAGACATACTGGAAAATGTTTCATGAGGTGATGGAAAT 1200
   -----+-----+-----+-----+-----+-----+-----+-----+
1201 CAAATTCAAAGGAGTGGACAATGAAGATGACCATGGCCGTGGAGACCTGGGGCGTCTCAA 1260
   -----+-----+-----+-----+-----+-----+-----+-----+
1261 GAAGCAAAAGGATCACCACAACCCACACCTGATCCTCATGATGATCCCCCACACCGACT 1320
   -----+-----+-----+-----+-----+-----+-----+-----+

```

Fig. 12

- 33/35 -

```

1321  GGACAGCCCAGGCCAGGGCAGTCAGAGGAAGAAGAGGGCCCTGGACACCAATTACTGCTT 1380
      -----+-----+-----+-----+-----+-----+-----+
1381  CCGCAACCTGGAGGAGAAGTGTGTACGCCCCCTTTATATTGACTTCCGGCAGGATCT 1440
      -----+-----+-----+-----+-----+-----+-----+
1441  AGGCTGGAAATGGGTCCACGAACCTAAGGGTTACTATGCCAACTTCTGCTCAGGCCCTTG 1500
      -----+-----+-----+-----+-----+-----+-----+
1501  CCCATACCTCCGCAGCGCAGACACAACCCATAGCACGGTGCTTGGACTATACAACACCCT 1560
      -----+-----+-----+-----+-----+-----+-----+
1561  GAACCCAGAGGGCGTCTGCCTCGCCATGCTGCGTCCCCCAGGACCTGGAGCCCCCTGACCAT 1620
      -----+-----+-----+-----+-----+-----+-----+
1621  CTTGTACTATGTGGGCAGAACCCCCAAGGTGGAGCAGCTGTCCAACATGGTGGTGAAGTC 1680
      -----+-----+-----+-----+-----+-----+-----+
1681  GTGTAAGTGCAGCTGAgggggatccactagttctagaggatccagacatgataagataca 1740
      -----+-----+-----+-----+-----+-----+-----+
1741  ttgatgagtttggacaaaaccacaactagaatgcagtgaaaaaaatgctttatttgtgaaa 1800
      -----+-----+-----+-----+-----+-----+-----+
1801  tttgtgatgctattgctttatttgaaccattataagctgcaataaacaagttaacaaca 1860
      -----+-----+-----+-----+-----+-----+-----+
1861  acaattgcattcatttttaigtgttcagggttcagggggaggtgtgggaggttttttaagca 1920
      -----+-----+-----+-----+-----+-----+-----+
1921  agtaaaacccctacaaaatgtggatggctgattatgacccctgcaagccctcgctcgtcggc 1980
      -----+-----+-----+-----+-----+-----+-----+
1981  cggaccacgctatctgtgcaagggtcccgggacggcgctccatgagcagagcgcccgcgg 2040
      -----+-----+-----+-----+-----+-----+-----+
2041  ccgaggcaagactcggggcgggcgcctgcccgtcccaccaggtcaacaggcggttaaccggc 2100
      -----+-----+-----+-----+-----+-----+-----+
2101  ctcttcacccggaatgcgcgcgaccttcagcatcgccggcatgtccctggcgagcggsa 2160
      -----+-----+-----+-----+-----+-----+-----+
2161  agtatcagctcgacnaagcttggcgagattttcaggagctaaggaagctaaaatggagaa 2220
      -----+-----+-----+-----+-----+-----+-----+
2221  aaaaatccactggarataccaccgttgatatatcccaatggcatcgtaaagaacattttga 2280
      -----+-----+-----+-----+-----+-----+-----+
2281  gycatttcagtcagttgctcaatgtacotataaccagaccgttcagctgcattaatgaat 2340
      -----+-----+-----+-----+-----+-----+-----+
2341  cggccaaacggcggggagaggcggtttgcgatattgggcgctcttcgcttcctcgctcac 2400
      -----+-----+-----+-----+-----+-----+-----+
2401  tgactcgctgcgctcggtcggttcggtgcggcgagcggtatcagctcactcaaagtcggt 2460
      -----+-----+-----+-----+-----+-----+-----+
2461  aatacyggttatccacagaatcaggggataacgcaggaaagaacatgtgagcaaaaggcca 2520
      -----+-----+-----+-----+-----+-----+-----+
2521  gcaaaaggccagggaaccgttaaaaaggccgcttgcgtggcggtttttccataggctccgccc 2580
      -----+-----+-----+-----+-----+-----+-----+
2581  ccccgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaaccgcagaggact 2640
      -----+-----+-----+-----+-----+-----+-----+

```

Fig. 12

Printed: 19-10-2001

SPEC

99116533

- 34/35 -

```

2641 ataaagataccaggcggtttccccctggaagctccctcgtgcgctctcctgttccgacctt 2700
-----+-----+-----+-----+-----+-----+-----+-----+
2701 gccgcttacggalacnctgtccgcctttctcccttcgggaagcgtggcgctttctcaatg 2760
-----+-----+-----+-----+-----+-----+-----+-----+
2761 ctcaagctgtaggtatctcagttcgggtgtaggtcgttcgctccaagctgggctgtgtgca 2820
-----+-----+-----+-----+-----+-----+-----+-----+
2821 cgaaccccccggttcagcccgancgctgccccttatccggtaactatcgtcttgagtccaa 2880
-----+-----+-----+-----+-----+-----+-----+-----+
2881 ccgggttaagacacgaacttatcgccactggaagcagccactggtaacaggattagcagagc 2940
-----+-----+-----+-----+-----+-----+-----+-----+
2941 gagggtatgtagggcgtgctacagagttcttgaagtggtggcctaactacggctacactag 3000
-----+-----+-----+-----+-----+-----+-----+-----+
3001 aaggacagtatttggtatctgcgctctgctgaagccagttaccttcggaaaaagagttgg 3060
-----+-----+-----+-----+-----+-----+-----+-----+
3061 tagctcttgatccggcaaaacaaaccacgcgtggtagcgggtggttttttggttgcaagca 3120
-----+-----+-----+-----+-----+-----+-----+-----+
3121 gcagattacgcgcagaaaaaaaggatctcaagaagatcccttgatctttctacggggtc 3180
-----+-----+-----+-----+-----+-----+-----+-----+
3181 tgacgctcagtggaacgaaaantcacgtaagggattttggtcatgagattatcaaaaag 3240
-----+-----+-----+-----+-----+-----+-----+-----+
3241 gatcttcacclagatcccttttaaatataaaatgaagttttaaatcaatctaaagtatata 3300
-----+-----+-----+-----+-----+-----+-----+-----+
3301 tgggtaaacttggctgacagttaccaatgcttaatcagtgaggcacctatctcagcgat 3360
-----+-----+-----+-----+-----+-----+-----+-----+
3361 ctgtctatttcgttcacccatagttgcctgaactcccgctcgtgtagataactacgatacg 3420
-----+-----+-----+-----+-----+-----+-----+-----+
3421 ggagggcttaccatcggccccagtgctgcaatgataccgcgagaccacgcctcaccggc 3480
-----+-----+-----+-----+-----+-----+-----+-----+
3481 tccagattcatcagcaataaaccagccagccggaaggccgagcgcagaagtggtcctgc 3540
-----+-----+-----+-----+-----+-----+-----+-----+
3541 aactttatccgcttcacatccagttctattaattggtgcccgggaagctagagtaagtagtcc 3600
-----+-----+-----+-----+-----+-----+-----+-----+
3601 gccagttaatagtttgccgaacggttggtgccattgctacaggcatcgtgtggtcacgctc 3660
-----+-----+-----+-----+-----+-----+-----+-----+
3661 gtcggtttggtatggcttcattcagctccgggttcccaacgatcaaggcgagttacatgac 3720
-----+-----+-----+-----+-----+-----+-----+-----+
3721 ccccatgttctgcaaaaaaqcggttagctccttcggtctccgatcgttgtcagaagtaa 3780
-----+-----+-----+-----+-----+-----+-----+-----+
3781 gttggccgcagtggttatcactcatggttatggcagcactgcataattctcttactgtcat 3840
-----+-----+-----+-----+-----+-----+-----+-----+
3841 gccatccgtaagatgctttctgtgactggtgagtaactcaaccaagtcattctgagaata 3900
-----+-----+-----+-----+-----+-----+-----+-----+
3901 gtgtatgcccgcaccgagttgctcttgcccgtcgtcaatacgggataataaccgcgccaca 3960
-----+-----+-----+-----+-----+-----+-----+-----+
tagcagaactttaaaagtgcctcatcattggaaaacgttcttcggggcgaaaactctcaag

```

Fig. 12

- 35/35 -

```
3961 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4020
      gatcttaccgctgttyagatccagttcgatgtaacccactcqtgcacccaactgatcttc
4021 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4080
      agcatcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggcaaaatgccgc
4081 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4140
      aaaaaaggggaataagggcgacacggaaatgttgaatactcatactcttccctttttcaata
4141 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4200
      ttatlgagcatttctcaggggttattgtctcatgagcggatacatatttgaatgtattta
4201 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4260
      gaaaaataaacaalaggggttccgcgcacatttccccgaaaagtgccacctgacgtcta
4261 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4320
      agaaaccattattatcatgacattaacctataaaaaataggcgtatcacgaggccctttcg
4321 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 4380
      tc
4381 -- 4382
```

Fig. 12

THIS PAGE BLANK (USPTO)